The American Journal of Medicine

EDITORIAL BOARD

The American Journal of Medicine

Editor: ALEXANDER B. GUTMAN, M.D.
Professor of Medicine
COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK
DIRECTOR, DEPARTMENT OF MEDICINE, THE MOUNT SINAI HOSPITAL, NEW YORK

Assistant Editors: MORTIMER E. BADER, M.D. AND RICHARD A. BADER, M.D.
THE MOUNT SINAI HOSPITAL, NEW YORK

ADVISORY BOARD

DAVID P. BARR, M.D.
Professor of Medicine
CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK

ARTHUR L. BLOOMFIELD, M.D.
Professor of Medicine, Emeritus
SCHOOL OF MEDICINE, STANFORD UNIVERSITY
SAN FRANCISCO

A. MCGEHEE HARVEY, M.D.
Professor of Medicine
JOHNS HOPKINS UNIVERSITY, SCHOOL OF MEDICINE
BALTIMORE

WALTER L. PALMER, M.D.
Professor of Medicine
UNIVERSITY OF CHICAGO, SCHOOL OF MEDICINE
CHICAGO

ASSOCIATE EDITORS

S. HOWARD ARMSTRONG, JR., M.D., *Chicago*
PAUL B. BEESON, M.D., *New Haven*
J. RUSSELL ELKINTON, M.D., *Philadelphia*
EUGENE B. FERRIS, JR., M.D., *Atlanta*
PETER H. FORSHAM, M.D., *San Francisco*
WILLIAM S. MCCANN, M.D., *Rochester, N. Y.*
GEORGE R. MENEELY, M.D., *Nashville*
CARL V. MOORE, M.D., *St. Louis*
JACK D. MYERS, M.D., *Pittsburgh*
ROBERT E. OLSON, M.D., *Pittsburgh*
DEWITT STETTEN, JR., M.D., *Bethesda*
JOHN V. TAGGART, M.D., *New York*
GEORGE W. THORN, M.D., *Boston*
ROY H. TURNER, M.D., *New Orleans*

The American Journal of Medicine is published monthly by The American Journal of Medicine, Inc., 49 West 45th Street, New York 36, N. Y. Yearly Subscription, $12.00 *U. S. A.;* $13.00 *Canada;* $15.00 *Foreign, including Latin-American countries, Single Numbers* $2.00; *Symposia Numbers* $4.00. *Entered as Second Class Matter June* 28, 1946, *at the Post Office, New York, N. Y., and on June* 28, 1946, *at York, Pa., under the act of March* 3, 1879. *February,* 1957—*Volume* XXII, *No.* 2. *Copyright* © 1957, *by The American Journal of Medicine, Inc.*

MANUSCRIPTS: All manuscripts should be addressed to the Editorial Office of the Journal, 49 West 45th St., New York 36, N. Y. *Style for bibliography:* Doe, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

Change of address must reach us one month preceding month of issue.

ADVERTISING REPRESENTATIVES

New York: Pliny A. Porter, Parker D. Brewer, H. Douglas Robinson
—JUDSON 2-3090

Chicago: R. H. Andrew, C. P. Haffner
—FRANKLIN 2-3861
Pasadena: Ren Averill—RYAN 1-9291

invitation to asthma?

not necessarily . . .

Tedral, taken at the first sign of attack, often forestalls severe symptoms.

relief in minutes . . . Tedral brings symptomatic relief in a matter of minutes. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

for 4 full hours . . . Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

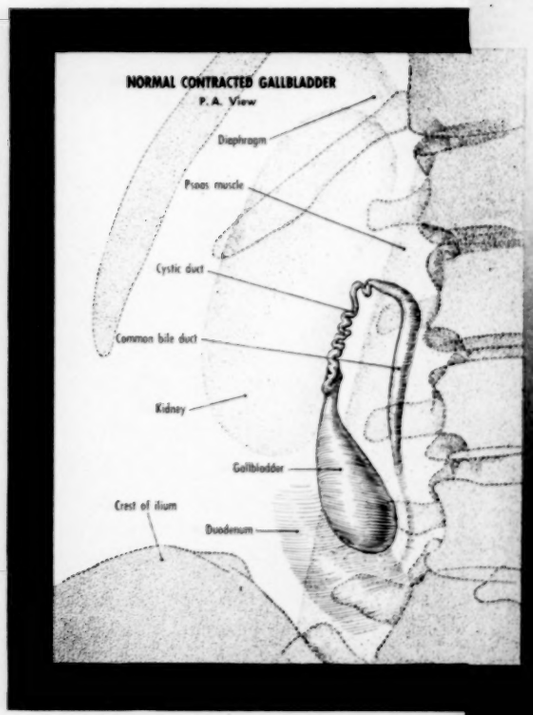
Tedral provides:

Theophylline	2 gr.
Ephedrine HCl	3/8 gr.
Phenobarbital	1/8 gr.

in boxes of 24, 120 and 1000 tablets

Tedral®

WARNER-CHILCOTT



"There are three main advantages in the use of

Telepaque®

SUPERIOR ORAL CHOLECYSTOGRAPHY AND CHOLANGIOGRAPHY

1. **Excellent cholecystograms are readily obtainable.**
2. **The side reactions are usually minimal, only rarely very disturbing, and often completely absent.**
3. **In a fairly large percentage of cases, the cystic and the common ducts are quite definitely outlined, and occasionally even the hepatic duct."**

Buckstein, Jacob: The Digestive Tract in Roentgenology. Philadelphia, J. B. Lippincott Co., 2nd ed., 1953, vol. 2, p. 1003.

DOSAGE:
The average adult dose of Telepaque is 3 Gm. (6 tablets). In persons of thin or medium build, weighing less than 150 lb., 2 Gm. (4 tablets) may be sufficient.

SUPPLIED:
Tablets of 0.5 Gm. in envelopes of 6 tablets, boxes of 5 and 25 envelopes, and bottles of 500.

Winthrop LABORATORIES
NEW YORK 18, N. Y. WINDSOR, ONT.

Telepaque (brand of iopanoic acid), trademark reg. U. S. Pat. Off.

CONTENTS

The American Journal of Medicine

Vol. XXII FEBRUARY, 1957 No. 2

Editorial

The Sympathetic Nervous System, the Vascular Volume and the Venous Return in Relation to Cardiovascular Integration. EDWARD D. FREIS AND JOHN C. ROSE 175

Clinical Studies

Kidney Function in Unilateral Pyelonephritis. I. Clinical Data
ALEXANDER J. MICHIE AND CATHARINE R. MICHIE 179

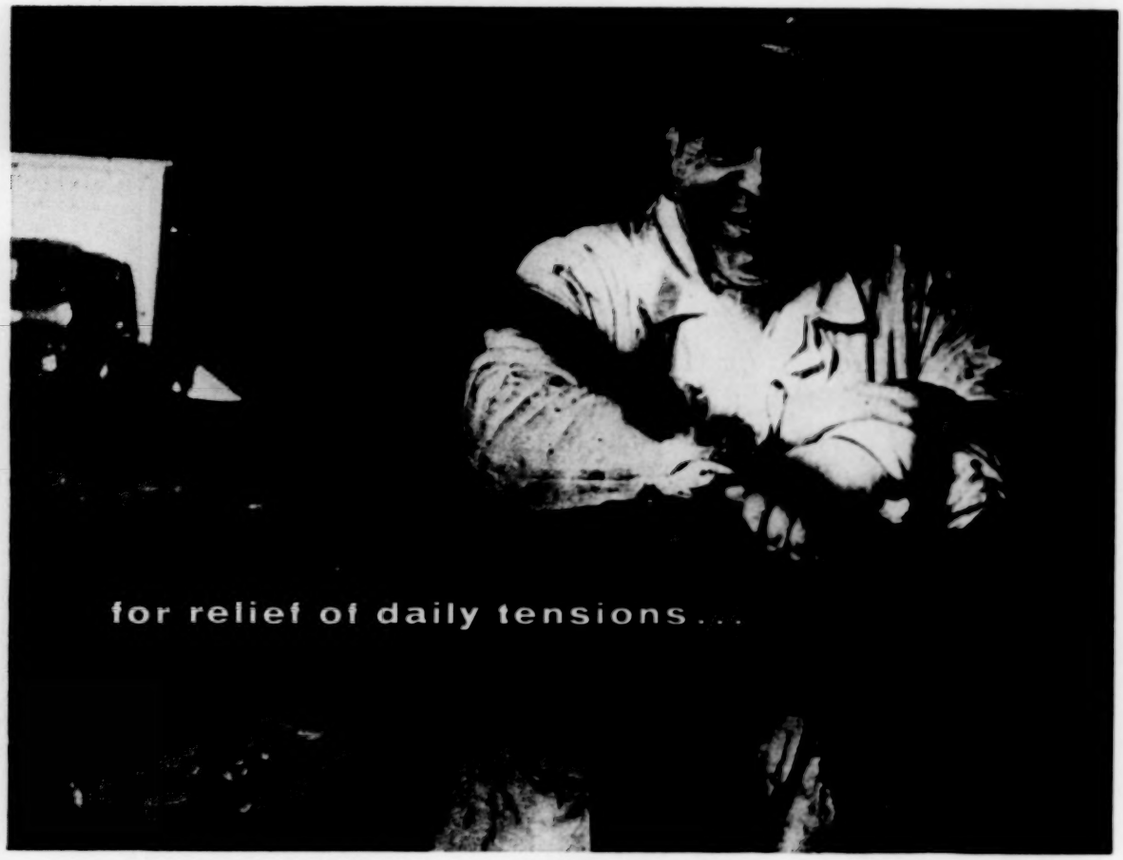
Kidney Function in Unilateral Pyelonephritis. II. Physiologic Interpretations
ALEXANDER J. MICHIE, CATHARINE R. MICHIE AND MARIE C. RAGNI 190

The authors apply the classic clearance methods for determination of glomerular filtration rate, effective renal plasma flow and Tm_{PAH} of the non-diseased and the diseased kidney in patients with unilateral pyelonephritis. Surprisingly little impairment in any of these measures of renal function was observed when pyelonephritis was of relatively short duration, in part because of hypertrophy of the non-diseased kidney and also of unaffected portions of the diseased kidney. When pyelonephritis is of long duration and more severe, particularly when there is ureteral obstruction by stone, the functional deficit may be marked. Analysis of the data brings out many other points of interest. This study doubtless is the most detailed of its kind yet reported. Nevertheless it should be appreciated that it is concerned essentially with hemodynamic data and does not take into account deficits in specific transport functions, for example, tubular reabsorption of various metabolites and electrolytes, which may occur in the diseased kidney.

The Valsalva Maneuver as a Test of Cardiac Function. Pathologic Physiology and Clinical Significance
RICHARD GORLIN, JOHN H. KNOWLES AND CAPT. CLIFFORD F. STOREY 197

In the normal subject the systemic arterial pressure during the Valsalva maneuver shows an initial rise followed by a fall in mean and pulse pressures with an overshoot upon cessation of the maneuver. In twenty-three patients with left or right ventricular failure or aortic or mitral stenosis an abnormal response to the Valsalva maneuver was noted. In an additional twenty-six patients an abnormal response also was obtained but only upon changing the body position. The abnormal response to the Valsalva maneuver is believed to reflect a flattened ventricular function curve. The authors state that use of the Valsalva maneuver in the way described affords a simple bedside test for detection of early left ventricular failure and of tight aortic and mitral stenosis in the absence of severe right ventricular failure.

Contents continued on page 5



a true calmative

nostyn®

Ectylurea, AMES
(higher melting isomer of
2-ethylcrotonylurea)

the power of gentleness

helps patients face everyday anxieties and tensions

*"...mild action promotes an over-all calmness..."**

New and Different • not a hypnotic-sedative—unrelated to any available chemo-psychotherapeutic agent • no evidence of cumulation or habituation • does not cause gastric hyperacidity • unusually wide margin of safety—no significant side effects

Dosage: 150-300 mg. three or four times daily.

Supplied: 300 mg. scored tablets, bottles of 48.

*Ferguson, J. T.: J. Am. Geriatrics Soc. *4*:1080, 1956.

AMES COMPANY, INC • ELKHART, INDIANA

24934

CONTENTS continued–February 1957

VOLUME TWENTY-TWO NUMBER TWO

Coronary Arteriovenous Fistula. Clinical and Physiologic Report on Two Patients, with Review of the Literature
RAYMOND J. WALTHER, GEORGE W. B. STARKEY, EVANGELINE ZERVOPOLUS AND GLEN A. GIBBONS 213

Two cases of coronary A-V fistula are presented, one diagnosed by means of venous cardiac catheterization. A review of eleven cases of this interesting anomaly reveals that shunting of coronary arterial blood may take place directly into the coronary sinus, right ventricle or pulmonary artery. The resulting clinical syndrome, particularly the murmur, may closely simulate patent ductus arteriosus. Pulmonary blood flow may be considerably increased, and electrocardiographic and radiographic evidence of ventricular hypertrophy is often seen. Life expectancy appears to be good. This anomaly should be considered in cases in which thoracotomy for patent ductus fails to reveal the expected lesion.

The Electrocardiogram in Atrial Septal Defect. A Study of Twenty-four Cases, with Observations on the RSR′-V1 Pattern . W. R. MILNOR AND C. A. BERTRAND 223

Investigation of a group of cases of atrial septal defect in which the anatomic diagnosis was confirmed by autopsy or surgical exploration showed that patients with the "ostium primum" type of defect complicated by a cleft and insufficient mitral valve can be recognized by the presence of left axis deviation and signs of both right and left ventricular hypertrophy in the electrocardiogram. Previous reports of the high incidence of the RSR′-V1 pattern in cases of atrial septal defect were confirmed, but it should be noted that the QRS duration may be entirely normal and that the same pattern often appears in other diseases with right ventricular hypertrophy.

Incomplete Transposition of the Great Vessels with Biventricular Origin of the Pulmonary Artery (Taussig-Bing Complex). Report of Four Cases and Review of the Literature . . . . . MICHELE A. CHIECHI 234

The Taussig-Bing complex was originally described as a rare member of the transposition anomalies, characterized by a transposed aorta, a large pulmonary artery arising principally from the right ventricle but partially overriding the ventricular septum and a high ventricular septal defect, with right ventricular hypertrophy. The present communication describes four such cases, two in great anatomic detail, and reviews the relevant literature describing the hemodynamic and clinical consequences of the malformation. The differential diagnosis of this form of cyanotic congenital heart disease due to transposition of the great vessels is set forth. Death ordinarily ensues early, with high output failure because of overloading of the low-pressure pulmonary circuit. However, the current great advances in cardiac surgery make possible correction even of this complex malformation.

The Cardiac Output in Paget's Disease before and after Treatment with Cortisone
ELLIOT RAPAPORT, HIROSHI KUIDA, LEWIS DEXTER, PHILIP H. HENNEMAN AND FULLER ALBRIGHT 252

The observation that massive doses of cortisone appear to have a temporarily suppressive effect on the metabolic process of osteitis deformans prompted study of the effect of this therapy on the cardiac output in six patients with extensive and active Paget's disease. Pretreatment cardiac

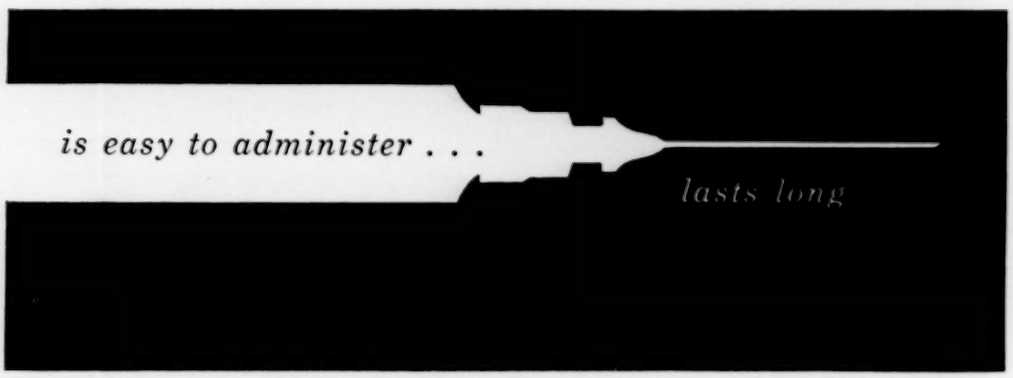
Contents continued on page 7

ACUTE EYE DISEASES

allergies

Economical treatment of the many conditions amenable to ACTH therapy

CORTROPHIN*-ZINC†



Use Cortrophin-Zinc to provide relief in the 100 or more conditions amenable to ACTH therapy. It's economical because each injection lasts at least 24 hours in the most acute cases, to 48 or even 72 hours in milder cases. It's easy to handle, too, because it is an aqueous suspension which flows freely through a 26-gauge needle with no preheating. Clinically proven in thousands of patients, an advance in ACTH therapy.

Available in 5-cc vials, each cc providing 40 U.S.P. units of corticotropin with 2.0 mg zinc.

*T.M.—Cortrophin

†Patent Pending. Available in other countries as Cortrophine-Z.

CORTROPHIN-ZINC
an Organon development

Organon INC.
ORANGE, N. J.

CONTENTS continued–February 1957

VOLUME TWENTY-TWO NUMBER TWO

outputs were uniformly although variably elevated and fell to normal levels during therapy. The results confirm previous observations that the cardiac output may be elevated in Paget's disease and are consistent with the suggestion that the increase is due to augmented blood flow through involved bones, resulting from innumerable arteriovenous shunts. The mechanism by which cortisone reduces this flow is unknown.

Essential Hyperlipemia. Report of Four Cases, with Special Reference to Abdominal Crises . . . . . Leo J. Corazza and Ralph M. Myerson 258

It has been well established that essential hyperlipemia, easily recognized by the presence of lactescent or milky serum in the fasting state (due to slow clearing), may manifest itself clinically by recurrent acute abdominal pain. In some instances the abdominal pain has been shown to be due to acute pancreatitis. A low fat diet helps, as indicated by illustrative case histories in this report.

Review

The Use of ACTH, Cortisone, Hydrocortisone and Related Compounds in the Management of Ulcerative Colitis. Experience in 180 Patients

Joseph B. Kirsner, Manuel Sklar and Walter L. Palmer 264

After early doubts and anxieties, steroid therapy of ulcerative colitis has found wide acceptance which is supported by substantial data now appearing from various sources. The present analysis of experience with 180 patients over a five-year period indicates that an immediate beneficial effect may be anticipated in about 85 per cent of cases but that eventual recurrence occurs in about 70 per cent, usually with repeated response to therapy. The net gain seems to justify the use of steroids in most instances, particularly since the incidence of such anticipated complications as peptic ulcer, hemorrhage, secondary infections and perforation appears to be surprisingly low.

Seminar on Bone Disease

Calcium and Phosphorus Metabolism . . . . . D. Harold Copp 275

Dr. Copp does not attempt a detailed review of the broad subject of calcium and phosphorus metabolism (appropriate references are cited) but limits the discussion to newer concepts, particularly as they have evolved from isotope exchange and turnover studies. The implications in respect to absorption, regulation of serum levels and the active metabolic role of the skeleton are especially emphasized. These aspects are oriented toward the clinical problems of bone disease but also bear directly upon broader problems of electrolyte regulation.

Clinico-pathologic Conference

Pyuria, Gross Hematuria, Convulsions and Possible Nephrotic Syndrome. 286

Clinico-pathologic Conference (Washington University School of Medicine)

Contents continued on page 9

PROVED...

in millions of doses
in millions of patients

Pentids

Squibb 200,000 Unit Buffered Penicillin G Potassium Tablets

t.

just 1 or 2 tablets

i.

d.

Effectiveness and **safety**
confirmed by five years' experience
in millions of patients

Convenient t.i.d. dosage—may be
given without regard to meals

Economical for the patient—
far less costly
than newer penicillin salts

Bottles of 12 and 100 tablets

SQUIBB

Squibb Quality—the Priceless Ingredient

'PENTIDS'® IS A SQUIBB TRADEMARK

CONTENTS continued–February 1957

VOLUME TWENTY-TWO NUMBER TWO

Case Reports

Polycyclic Nephrotic Syndrome . . . DAVID A. RYTAND AND ALVIN J. COX, JR. 297

Recurrence of the full-blown nephrotic syndrome after disappearance of proteinuria is distinctly unusual in Bright's disease. The authors cite a carefully studied case with eight such recurrences. Necropsy showed membranous glomerulonephritis with glomerular adhesions and fibrosis. These findings, the authors point out, need not be indicative of Bright's disease but, taken in context with the clinical course, may be considered to be consistent with lipemic nephrosis with associated membranous glomerulonephritis.

Hypertension Due to Segmental Infarction of the Kidney
J. ALEX HALLER, JR., LEO R. RADIGAN AND ANDREW G. MORROW 303

A well documented case of unilateral renal disease (segmental infarction due to embolus) producing hypertension, which was reversed following nephrectomy. Brief discussion of this case as an example of the Goldblatt phenomenon is presented.

Tricuspid Stenosis. Report of a Case, with Hemodynamic Studies at Tricuspid Commissurotomy
ALVIN J. GORDON, GABRIEL GENKINS, ARTHUR GRISHMAN AND ROBERT A. NABATOFF 306

The authors made full use of a rare opportunity to study the hemodynamics of isolated tricuspid stenosis, not only by the usual technics but also by simultaneous right atrial and ventricular pressure recordings at the time of tricuspid commissurotomy. The hemodynamic relationships correspond, in general, to those anticipated from similar observations in mitral stenosis but differ in several respects, the significance of which is interestingly pointed out.

Hemorrhagic Disease in Osteogenesis Imperfecta. Study of Platelet Functional Defect
BERNARD M. SIEGEL, IRVING A. FRIEDMAN AND STEVEN O. SCHWARTZ 315

An interesting case report and discussion of the presence of a deficiency in the thromboplastic function of platelets, with associated bleeding tendency, in a patient with osteogenesis imperfecta. It is suggested that this concurrence of two rather rare anomalies, both representing mesenchymal defects, is not altogether coincidental.

Chronic Erythrocytic Hypoplasia in Adults. Review of Literature and Report of a Case
SHIH YUAN TSAI AND WILLIAM C. LEVIN 322

The subject of this report is a syndrome, rare in the adult, characterized by profound anemia, virtual absence of red cell precursors in the bone marrow while the leukocyte and megakaryocyte series is normal, no extramedullary hemopoiesis, no hemorrhagic manifestations. Of interest is the association with thymoma in more than 25 per cent of the cases.

Pulseless Disease . . . . . JANET R. KINNEY 331

An interesting example of a curious syndrome.

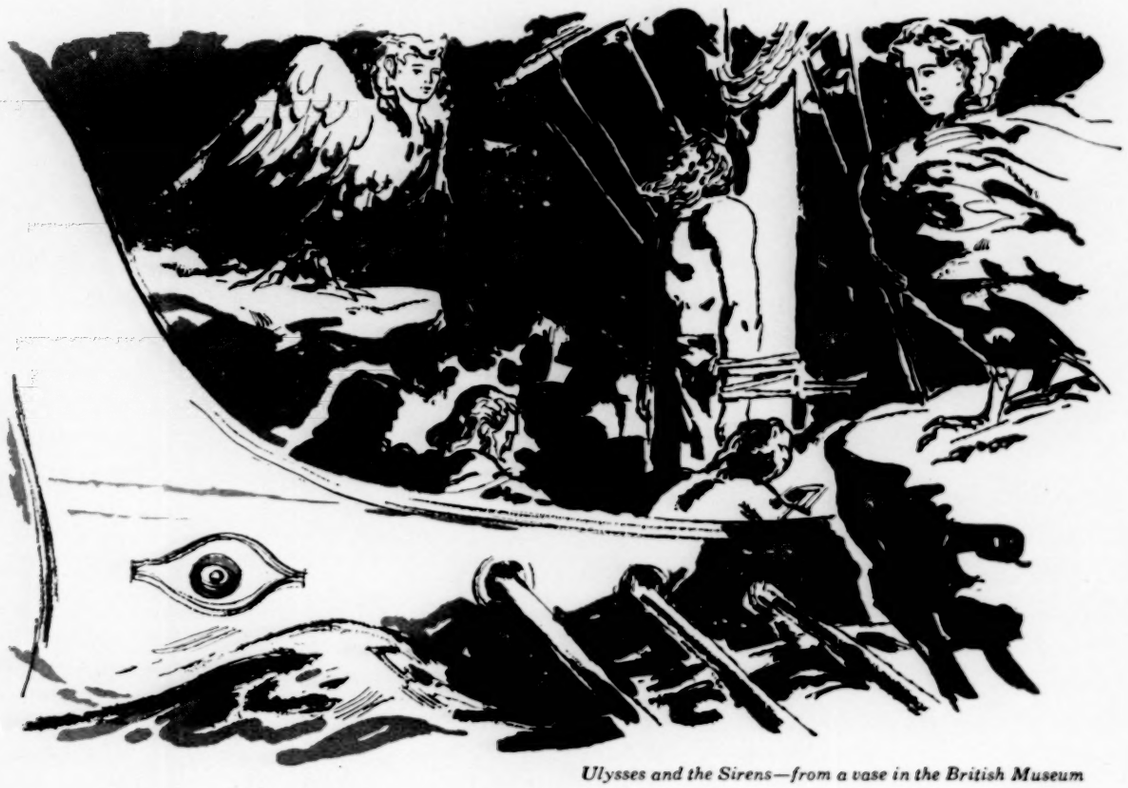
Intrathoracic Meningocele
RICHARD R. MOYER, HARRY R. CRAMER AND GARFIELD G. DUNCAN 334

An interesting case.

Advertising Index on Page 93

Change of address must reach us one month preceding month of issue.

In the arthritides . . . a prudent course



Ulysses and the Sirens—from a vase in the British Museum

between the hazards of high steroid dosage
and the frustration of inadequate relief

Because of the complementary action of cortisone and the salicylates, Salcort produces a greater therapeutic response with lower dosage.

One study concludes: "Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

SALCORT®*

indications:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Neuromuscular affections.

[1]Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. *11*:1105.

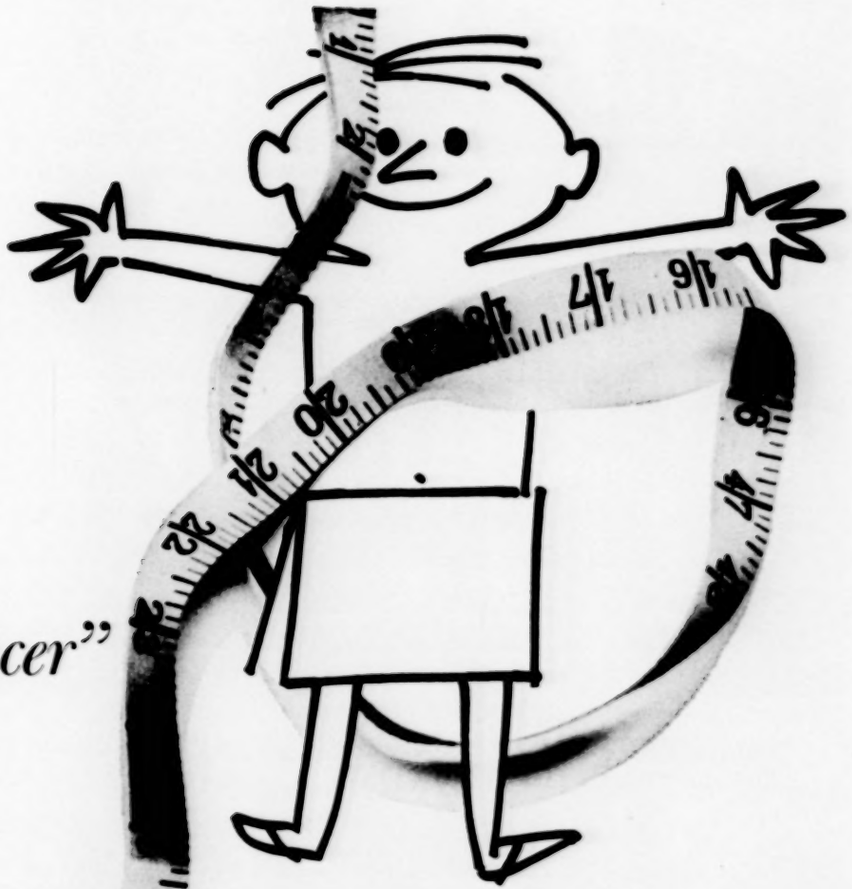
each tablet contains:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried . . .	0.12 Gm.
Calcium ascorbate . . . . . (equivalent to 50 mg. ascorbic acid)	60.0 mg.
Calcium carbonate	60.0 mg.

**U.S. Pat. 2,691,662*

The S. E. MASSENGILL Company, Bristol, Tennessee

NEW YORK • KANSAS CITY • SAN FRANCISCO



keep
the "reducer"
happy

'Methedrine'

brand Methamphetamine Hydrochloride

'Methedrine' dispels abnormal craving for food, and subtly elevates the mood. Reducing diets are accepted easily, without frustration.

'Methedrine' is safe, in recommended doses, for pregnant women.

'Methedrine' brand Methamphetamine Hydrochloride Tablet of 5 mg., scored.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

NEW! *More Effective...*

Medihaler-Phen™

Unvarying Measured-Dose Nasal Medication Reaching the Entire Paranasal Mucosa

VASOCONSTRICTIVE Counteracts hyperemia of nasal and paranasal mucosa

DECONGESTIVE Diminishes edema and hypersecretion . . . opens sinus ostia

ANTI-INFLAMMATORY Neutralizes the exudative phase of tissue reaction

ANTIBIOTIC Attacks bacterial invasion directly

Medihaler-Phen™ . . . an ethical prescription item . . .

makes squeeze bottle and dropper medications obsolete

Medihaler-Phen is self-powered, measured-dose vaporized medication providing effective relief for congested nasal and paranasal mucosa.

Its active ingredients — phenylephrine HCl, hydrocortisone, and neomycin sulfate — are in wide clinical use. In Medihaler-Phen, for the first time, they are blended with an inert, nontoxic aerosol propellent, and are made more effective with a penetrating surfactant. An accurately-measured nebular cloud is gently ejected, regardless of how the Medihaler-Phen valve is compressed — not part spray, part stream as with spray bottles — not an irritating, powerful jet — no drops of liquid which tend to run out of the nasal passages.

Because of the extremely small, uniform particle size of Medihaler-Phen nebulization, less medication is required to decongest the mucosa and open the ostia of paranasal sinuses.

Longer Lasting Relief in Nasal Congestion

RHINITIS
SINUSITIS
PHARYNGITIS

due to upper respiratory infections and allergies

tissue compatible
greater effectiveness
longer lasting
no rebound
vest pocket size

Medihaler-Phen™ is Safe

...FOR CHILDREN, TOO

Repeated use does not result in tachyphylaxis. . . . Does not possess the cardiac and nervous system-stimulating actions characteristic of other topical vasoconstrictors. . . . Even gross overdosage does not lead to drowsiness or deep somnolence in children. . . . Concentration of hydrocortisone effective locally, but produces no systemic effect. . . . Penetrates "mucous blanket" of nasal mucosa without irritation.

OTHER USES Medihaler-Phen is also valuable in the symptomatic treatment of "postnasal drip" due to excessive smoking, air pollution, steam heating, etc.

ANOTHER Riker FIRST

A good start for safer bowel surgery

PHTHALYLSULFATHIAZOLE

The virtual "sterilization" of pathogenic bowel contents which follows preoperative administration of SULFATHALIDINE eliminates a major danger in intestinal surgery. Postoperatively, SULFATHALIDINE continues the suppression of dangerous pathogens, lessens the likelihood of peritonitis and abscess formation. Flatus is minimal; fungi and yeast do not overgrow their habitat; early healing is promoted. SULFATHALIDINE is an important adjunct in ulcerative colitis.

CREMOTHALIDINE® is a palatable suspension of SULFATHALIDINE. Each 30 cc. (1 fluidounce) contains 6.0 Gm. SULFATHALIDINE.

MSD

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

when
you
prescribe

Pentobarbital sodium and Carbromal. In Kapseal® and Elixir form.

you
prescribe
sleep

Erythromycin in Treating Pneumonia

A 27-year-old man, a chronic alcoholic, was admitted with a history of an alcoholic spree followed by a cough, greenish sputum and chills and fever.

Physical examination showed a temperature of 104 F. and indicated pneumonia in the right lower lobe. This was confirmed by X-ray. The sputum revealed gram-positive diplococci and blood culture subsequently grew Type VII pneumococci.

The patient was treated with erythromycin, 300 mg. every six hours per os. His temperature dropped to normal by 48 hours and X-ray of the chest revealed considerable clearing by the fourth hospital day. After 10 days hospitalization, the patient was fit for discharge.[1]

First Antibiotics Symposium, we reported the successful treatment with thromycin of *H. influenzae* pneumonia and bacteremia. A second patient with *H. influenzae* pneumonia and bacteremia had a clinical course almost identical to the one previously reported, with cure obtained by treatment with 500 mg. of erythromycin per os every four hours for 14 days.

Of these 132 patients with bacterial pneumonia, 127 (96%) had a good clinical result. One patient with lobar pneumonia had a good initial response but had delayed resolution after treatment.

"Highly Effective in Pneumonia"

In one investigation, 75 adult patients with bacterial pneumonia were treated with erythromycin. In his summary, the clinician reported: "It is concluded that erythromycin is highly effective in the treatment of pneumonia due to gram-positive bacteria."[2]

This, of course, is only one of many reports showing the effectiveness of ERYTHROCIN against coccic infections. You'll get the same good results (nearly 100% in common, bacterial respiratory infections) when you prescribe ERYTHROCIN. Abbott

filmtab®

Erythrocin®

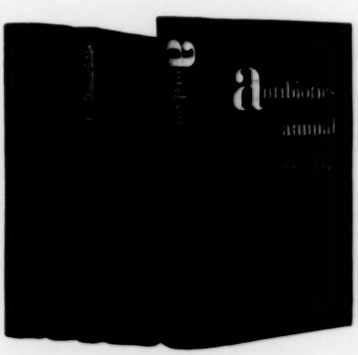
(Erythromycin, Abbott)

STEARATE

"No Serious Side Effects Occurred"

After a study of 171 patients treated with erythromycin, the investigator wrote: "No serious side effects occurred with prolonged therapy or with doses up to 8 Gm. per day in the severe infections."[1]

Actually, ERYTHROCIN stands on a remarkable record of safety. After four years, there's not a single report of a severe or fatal reaction attributable to erythromycin. In addition, you'll find allergic manifestations rarely occur. *Filmtub* ERYTHROCIN Stearate (100 and 250 mg.), in bottles of 25 and 100. Abbott



® Filmtab—Film-Sealed tablets, Abbott; pat. applied for.

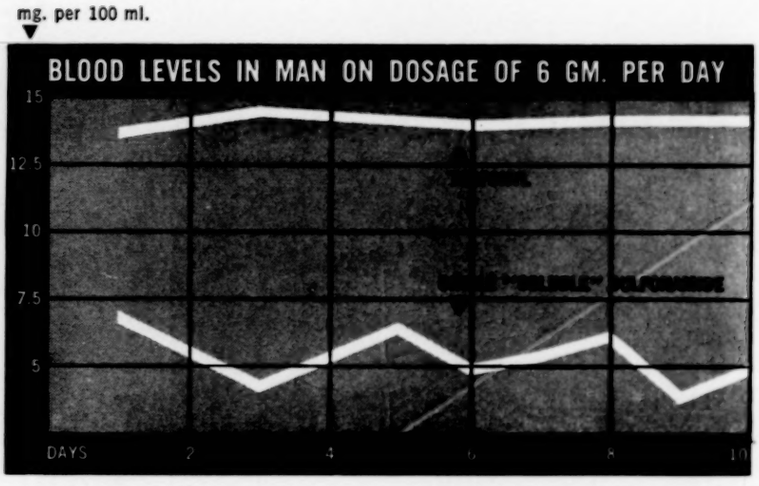
1. Romansky, M.J., et al., Antibiotics Annual 1955-1956, p. 48.
2. Waddington, W. S., Maple, F. C., and Kirby, W. M. M., A.M.A. Archives of Internal Medicine, 1954, p. 556.

701051

maximum efficacy with minimum risk

Terfonyl

SQUIBB METH-DIA-MER SULFONAMIDES



— After Lehr, D., Modern Med. 23:111 (Jan. 15) 1955.

Terfonyl is absorbed as well as single "soluble" sulfonamides, but is eliminated at a slower rate. For this reason, Terfonyl blood levels are much higher.

In experimental infections (Klebsiella, Pneumococcus, Streptococcus), Meth-Dia-Mer sulfonamides have been shown to be from three to four times more effective on a weight basis than single "soluble" sulfonamides.

Toxicity is minimal because normal dosage provides only one-third the normal amount of each sulfonamide. The body handles each component as though it were present alone, although therapeutic effects are additive.

Terfonyl Tablets, 0.5 Gm., bottles of 100 and 1000.
Terfonyl Suspension, 0.5 Gm. per 5 ml., pint bottles.

0.167 Gm. each of sulfamethazine, sulfadiazine and sulfamerazine per tablet or per 5 ml. teaspoonful of suspension.

SQUIBB

'TERFONYL'® IS A SQUIBB TRADEMARK

blue at breakfast?

BONADOXIN®

(brand of meclizine dihydrochloride and pyridoxine hydrochloride)

stops morning sickness

manifest in 3 out of every 4 pregnancies. Relief with BONADOXIN was over 90% in controlled studies, which termed results "good to excellent."[1,2,3,4] . . . tolerance "excellent."[1] Complete relief is often afforded "within a few hours."[2]

Each BONADOXIN *tablet contains:*

Meclizine HCl	25 mg.
Pyridoxine HCl	50 mg.

In mild cases, one BONADOXIN tablet at bedtime. Severe cases, one tablet at bedtime and on arising.

Supplied: Tiny pink and blue tablets, bottles of 25 and 100 . . . prescription only.

. . . and as pre-natal supplementation,

STORCAVITE®

the new, phosphate-free formula, which brings the gravida vitamin-mineral supplementation and full-term freedom from leg cramps.†

Rx: one tablet t.i.d.—p.c.

STORCAVITE® (comprehensive formula of vitamins A, B complex, C, D, E and of minerals, phosphate-free)

Supplied: Orange-colored, sugar-coated tablets, bottles of 100.

†when due to high phosphorus intake

ROERIG

Chicago 11, Illinois

PEACE of mind ATARAX®

REFERENCES: 1. Weinberg, A. and Werner, W.E.F.: Am. Pract. & Dig. Treat. **6**:580, 1955. 2. Groskloss, H.H. et al: Clin. Med. **2**:885, 1955. 3. Crawley, C. R.: West. J. Surg. Gynec. and Obst. **8**:463 (Aug.) 1956. 4. Tartikoff, G.: Clin. Med. **3**:223 (Mar.) 1956.

sparine*

HYDROCHLORIDE

10-(γ-dimethylamino-n-propyl)-phenothiazine hydrochloride

*Trademark

Promazine Hydrochloride

THE ALCOHOLIC

SPARINE is an agent of prompt, predictable, and potent action in controlling withdrawal symptoms.
Often, in selected cases under the adequate supervision of the family physician, it may afford *home control* of postalcoholic agitation and hyperactivity.[1]

SPARINE is well tolerated on intravenous, intramuscular, or oral administration.
Toxicity is minimal—no case of liver damage has been reported. Parenteral use offers (1) minimal injection pain; (2) no tissue necrosis at the injection site; (3) potency of 50 mg. per cc.; (4) no need for reconstitution before injection.

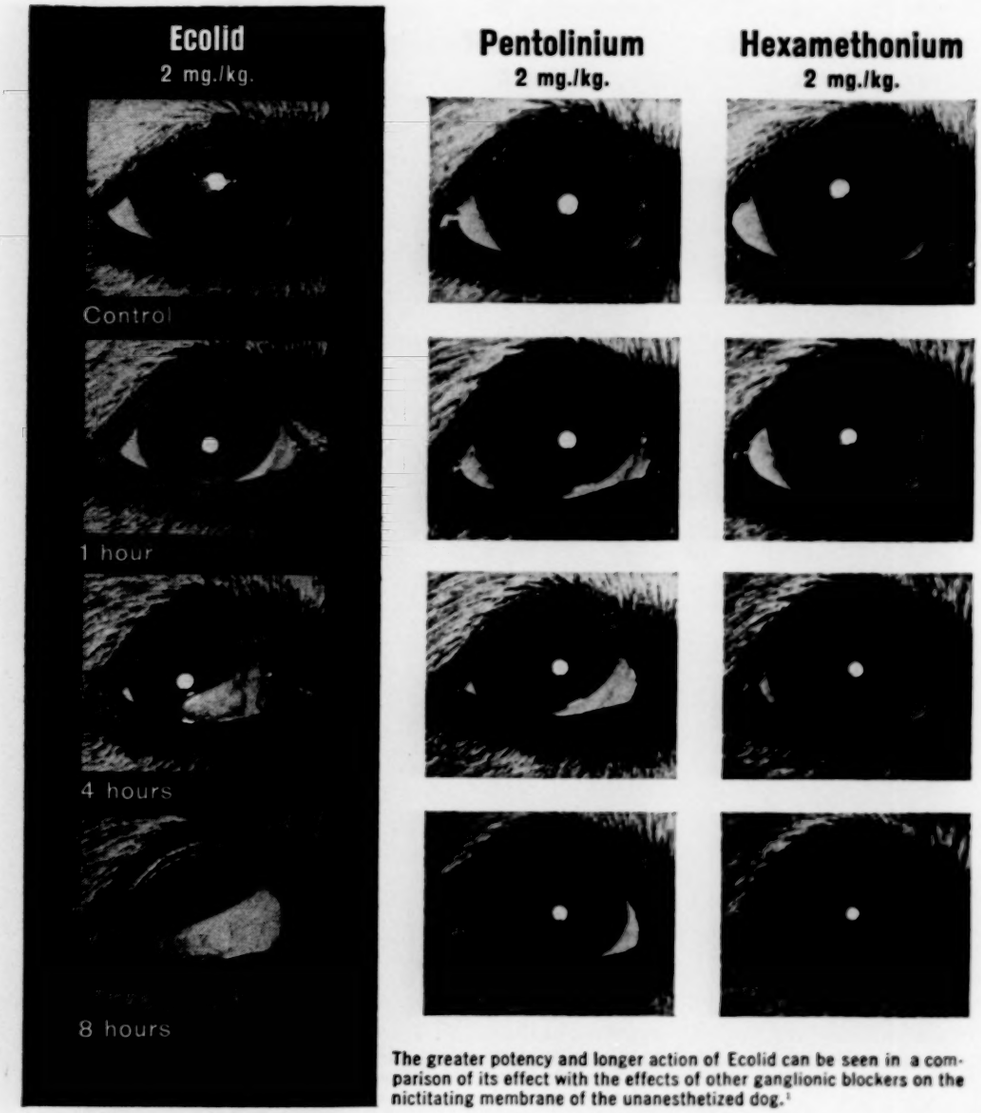
Professional literature available upon request.

1. Figurelli, F.A.: Indust. Med. & Surg. 25:376 (Aug.) 1956.

Wyeth

Philadelphia 1, Pa.

When less potent antihypertensives fail . . .



The greater potency and longer action of Ecolid can be seen in a comparison of its effect with the effects of other ganglionic blockers on the nictitating membrane of the unanesthetized dog.[1]

Ecolid®

chloride

(chlorisondamine chloride CIBA)

CIBA
SUMMIT, N. J.

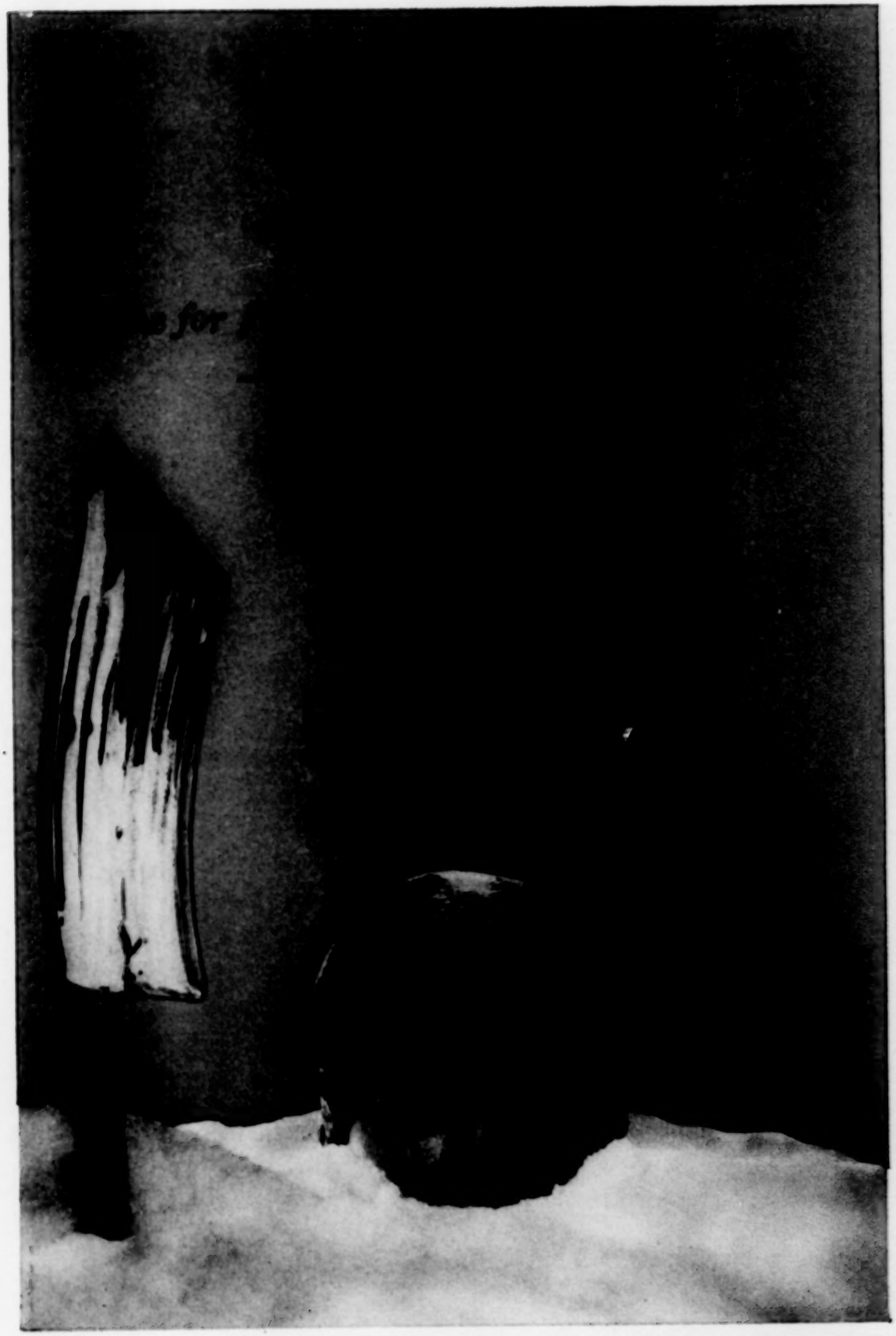
Clinically, reduction in blood pressure instituted with Ecolid was more effective, more consistent and more prolonged at a lower oral dosage than with other ganglionic blockers, including hexamethonium and pentolinium.[2-4] Patients preferred Ecolid to hexamethonium "... for reasons varying from relief of constipation to need to take fewer tablets a day."[4] Ecolid is recommended in moderate, severe, even malignant hypertension.

For complete information on dosage recommendations, management of side effects and precautions, please write Medical Service Division for booklet entitled *"Ecolid — A New Ganglionic Blocker for Hypertension."*

1. Plummer, A. J., Trapold, J. H., Schneider, J. A., Maxwell, R. A., and Earl, A. E.: J. Pharmacol. & Exper. Therap. 115:172 (Oct.) 1955. 2. Grimson, K. S.: J.A.M.A. 158:359 (June 4) 1955. 3. Smith, J. R., and Hoobler, S. W.: Univ. Michigan M. Bull. 22:51 (Feb.) 1956. 4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation 11:733 (May) 1955.

Supplied: **Ecolid Tablets (Rotocotes), 25 mg. (ivory) and 50 mg. (pink).**

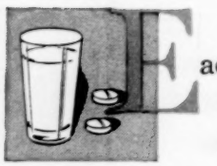
ROTOCOTES T.M. (dry-compressed, coated tablets CIBA)



In Angina Pectoris

The Attacks Lessen and The Patient Loses His Fear

Pentoxylon®



Each long-acting tablet provides the sustained coronary vasodilating effect of 10 mg. pentaerythritol tetranitrate (PETN) as well as the tranquilizing, anxiety-relieving and pulse-normalizing action of 1 mg. Rauwiloid® (alseroxylon).

- Reduces incidence of attacks
- Reduces severity of attacks
- Reduces or abolishes need for fast-acting vasodilating drugs
- Reduces tachycardia
- Reduces blood pressure in hypertensives, not in normotensives
- Increases exercise tolerance
- Produces demonstrable ECG improvement
- Exceptionally well tolerated
- Minimal side actions
- Dosage: one to two tablets q.i.d., a.c. and h.s.

And

for faster relief of the acute attack

Medihaler-Nitro®

octyl nitrite (1%) in aerosol solution

For faster, safer, and more lasting relief of acute anginal attacks . . . Measured-dose inhalation provides instantaneous coronary vasodilatation via the lungs . . . one inhalation equivalent to 1/100 gr. nitroglycerin . . . fewer side actions than amyl nitrite . . . pocket-sized aerosol set . . . each 10 cc. bottle delivers 200 metered doses.

Riker

LOS ANGELES

Announcing
a new
antibacterial
with
double-spectrum
action—

A new antibacterial

with double-spectrum action

plus a high degree of safety

Gantrimycin

'ROCHE'

Why is Gantrimycin so effective? Because it provides Gantrisin plus oleandomycin (a new antibiotic) which mutually reinforce each other; and there is a high degree of safety plus a pronounced effect on most pathogens resistant to other antibiotics.

The double-spectrum action of Gantrimycin is valuable against both gram-positive and gram-negative microorganisms.

Dosage: Adults—2 to 3 tablets, four times daily; should be increased to 4 or 5 tablets, four times daily, if necessary. Children over 30 lbs—1 or 2 tablets, four times daily. Children under 30 lbs—1 tablet, four times daily.

Each blue Gantrimycin tablet contains 333 mg Gantrisin and 75 mg oleandomycin.

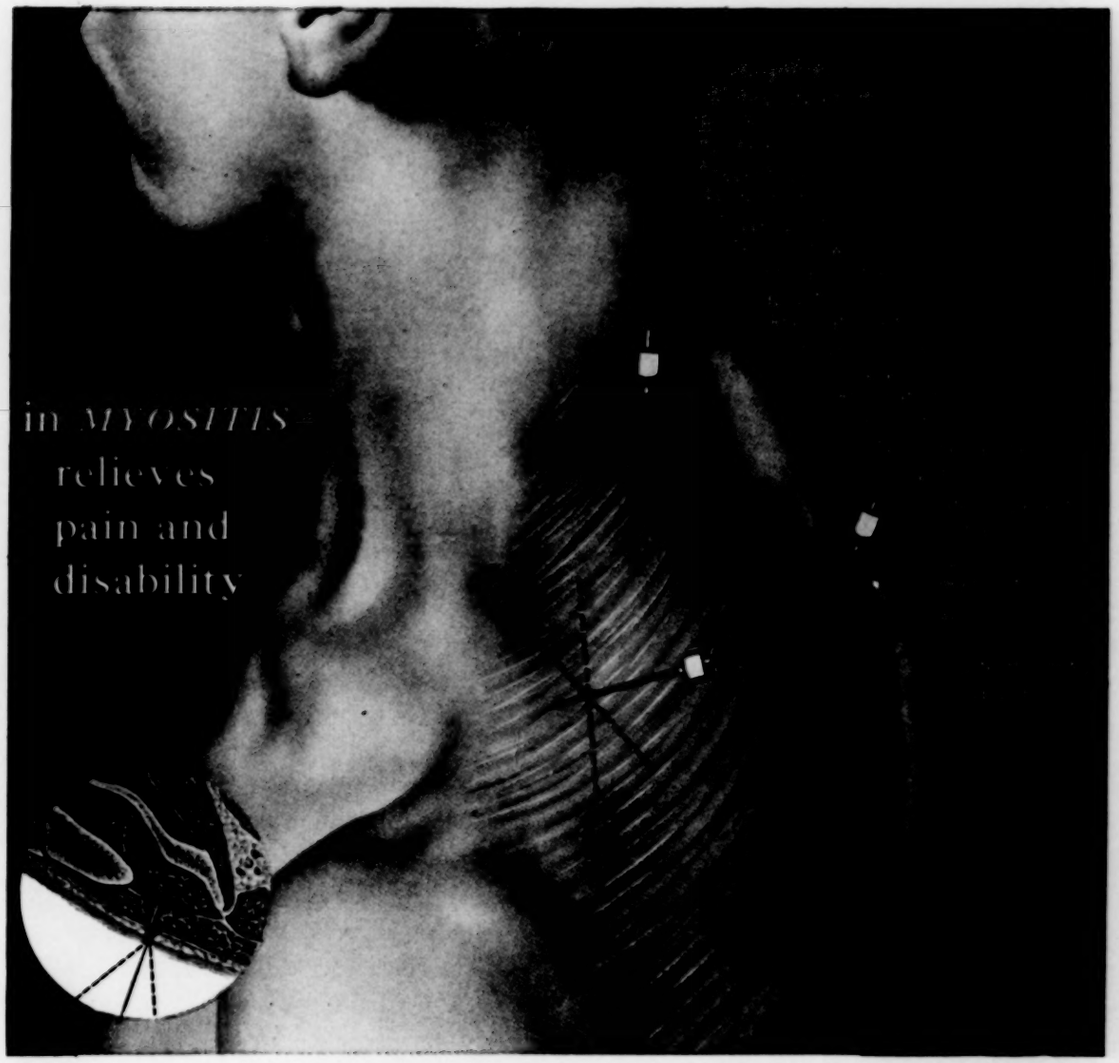
Gantrisin®; Gantrimycin™

HOFFMANN-LA ROCHE INC • Nutley 10 • New Jersey

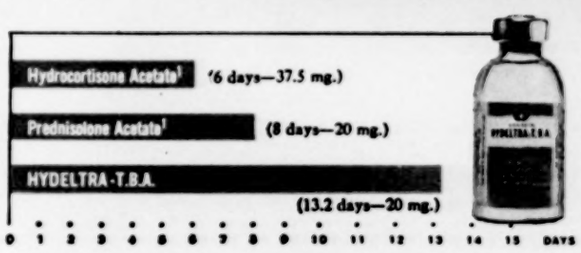
NEW HYDELTRA® -T.B.A.

(Prednisolone *tertiary*-butylacetate, Merck)

for relief that lasts—longer



Anti-inflammatory effect lasts longer than that provided by any other steroid ester


Hydrocortisone Acetate[1]
(6 days—37.5 mg.)
Prednisolone Acetate[1]
(8 days—20 mg.)
HYDELTRA-T.B.A.
(13.2 days—20 mg.)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 DAYS

Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

Supplied: Suspension 'HYDELTRA'-T.B.A.—20 mg./cc. of prednisolone *tertiary*-butylacetate, in 5-cc. vials.

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PA.

1. Hollander, J. L., *Paper read at conference in New York City, May 31 and June 1, 1955*

Liquid Pediatric Drops

aqueous suspension

stabilized, soluble, no oil to block absorption, no oily taste or repeat, remarkably free of side effects

ready-to-use, no refrigeration

freely miscible in water, milk, formula, or drop directly on tongue

handy, plastic dropper bottle

accurate dosage is easy, one drop per pound body weight per day

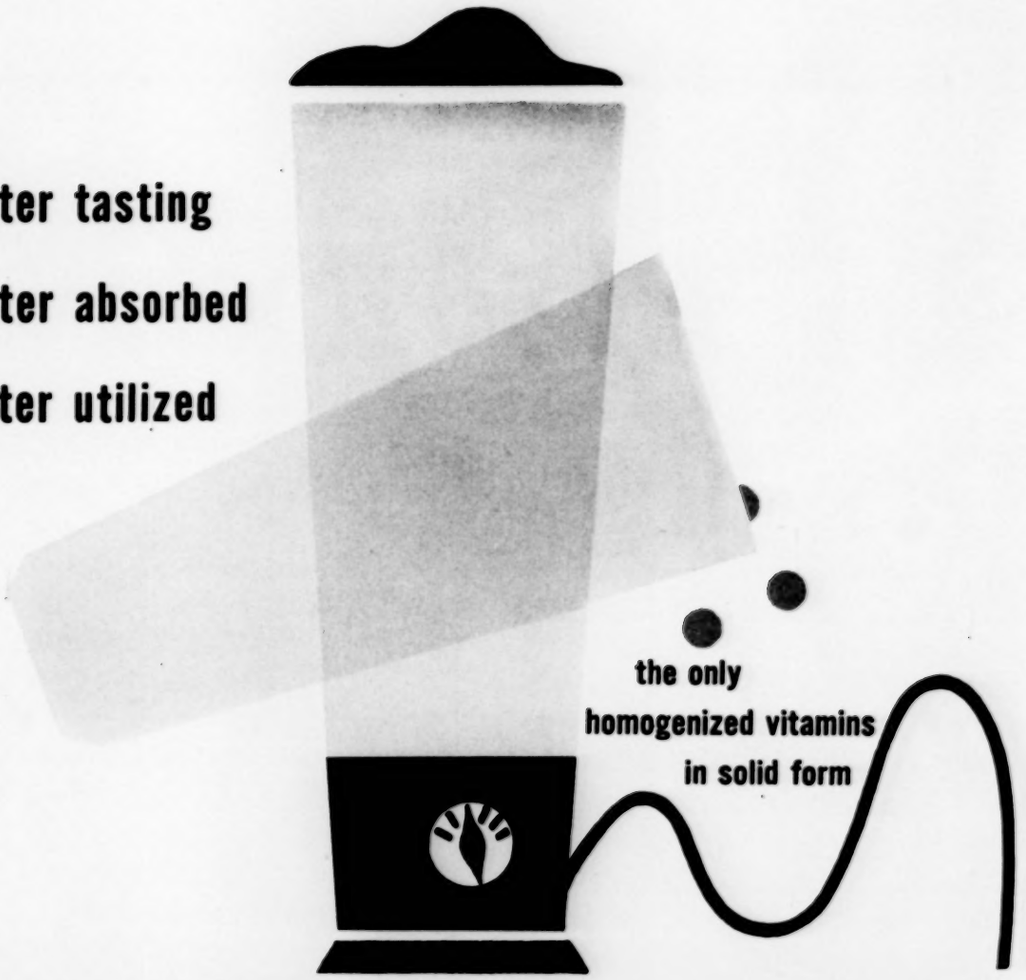
Supplied: 10 cc. plastic dropper-type bottle (cherry-flavor), 100 mg./cc. (approx. 5 mg. per drop)

ACHROMYCIN* Tetracycline ranks among the foremost in its field today... judged on its exceptional effectiveness against a wide range of pathogens, prompt control of infections commonly seen in medical practice, low incidence of side reactions. These outstanding features have been repeatedly confirmed by physicians everywhere during more than three years of clinical usage.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, N. Y.
*Reg. U. S. Pat. Off.

Lederle

ACHROMYCIN...ACKNOWLEDGED FOR COMPETENCE



HOMAGENETS®*

Homagenets provide multivitamins in the same way as do the most nutritious foods. By a unique process, the vitamins are homogenized, then fused into a solid, highly palatable form. Compare the taste of Homagenets with other vitamin preparations.

Homogenization presents both oil and water soluble vitamins in microscopic particles. This permits greater dispersion of the vitamins—thus better absorption and utilization. And the flavorful base assures patient acceptance.

*U.S. Pat. 2676136. Other Pat. Pending

Advantages—

Better absorption, better utilization

Excess vitamin dosage unnecessary

Pleasant, candy-like flavor

No regurgitation, no "fishy burp"

May be chewed, swallowed or dissolved in the mouth

Three formulas:

Prenatal Pediatric Therapeutic

Send for samples of Homagenets. Taste them, and compare.

The S. E. MASSENGILL Company

BRISTOL, TENNESSEE · NEW YORK · KANSAS CITY · SAN FRANCISCO

WHEN
COUGH
OCCURS with colds or allergies

AMBENYL® EXPECTORANT

relieves cough
and controls congestive symptoms

contains demulcent and expectorant agents plus
AMBODRYL® for antihistaminic action
BENADRYL® for antihistaminic-antispasmodic effect

Supplied: 16-ounce and 1-gallon bottles

AMBODRYL Hydrochloride (bromodiphenhydramine hydrochloride, Parke-Davis)
BENADRYL Hydrochloride (diphenhydramine hydrochloride, Parke-Davis)

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

Now Simplified dosage* to prevent Angina Pectoris

Metamine®

Triethanolamine trinitrate biphosphate, LEEMING, 10 mg.

Sustained

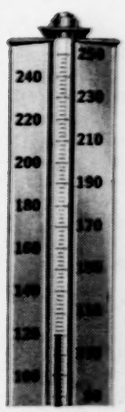
***Usual dose:** Just 1 tablet upon arising and one before the evening meal. Bottles of 50 tablets. THOS. LEEMING & CO., INC., 155 East 44th Street, N.Y. 17, N.Y.

Hypertensive Objective: **ACTIVE LIVING**

. . . from incapacitating hypertension to a life of usefulness.

Case History:[1] A.B., 42-year-old hospitalized patient with severe hypertension and early heart failure. Blood pressure prior to treatment was 240/160 mm. Hg. ANSOLYSEN was administered orally t.i.d. The dose was adjusted to the patient's requirements. Blood pressure was reduced to, and stabilized at, an average level of 150/105 mm. Hg. There was marked symptomatic improvement, and the patient was able to return to work.

1. Case history on file in Medical Department of Wyeth Laboratories.



ANSOLYSEN®

TARTRATE — **Pentolinium Tartrate**

Lowers Blood Pressure

Wyeth®
Philadelphia 1, Pa.

announcing

LIPO GANTRISIN

'Roche'

For round-the-clock therapy

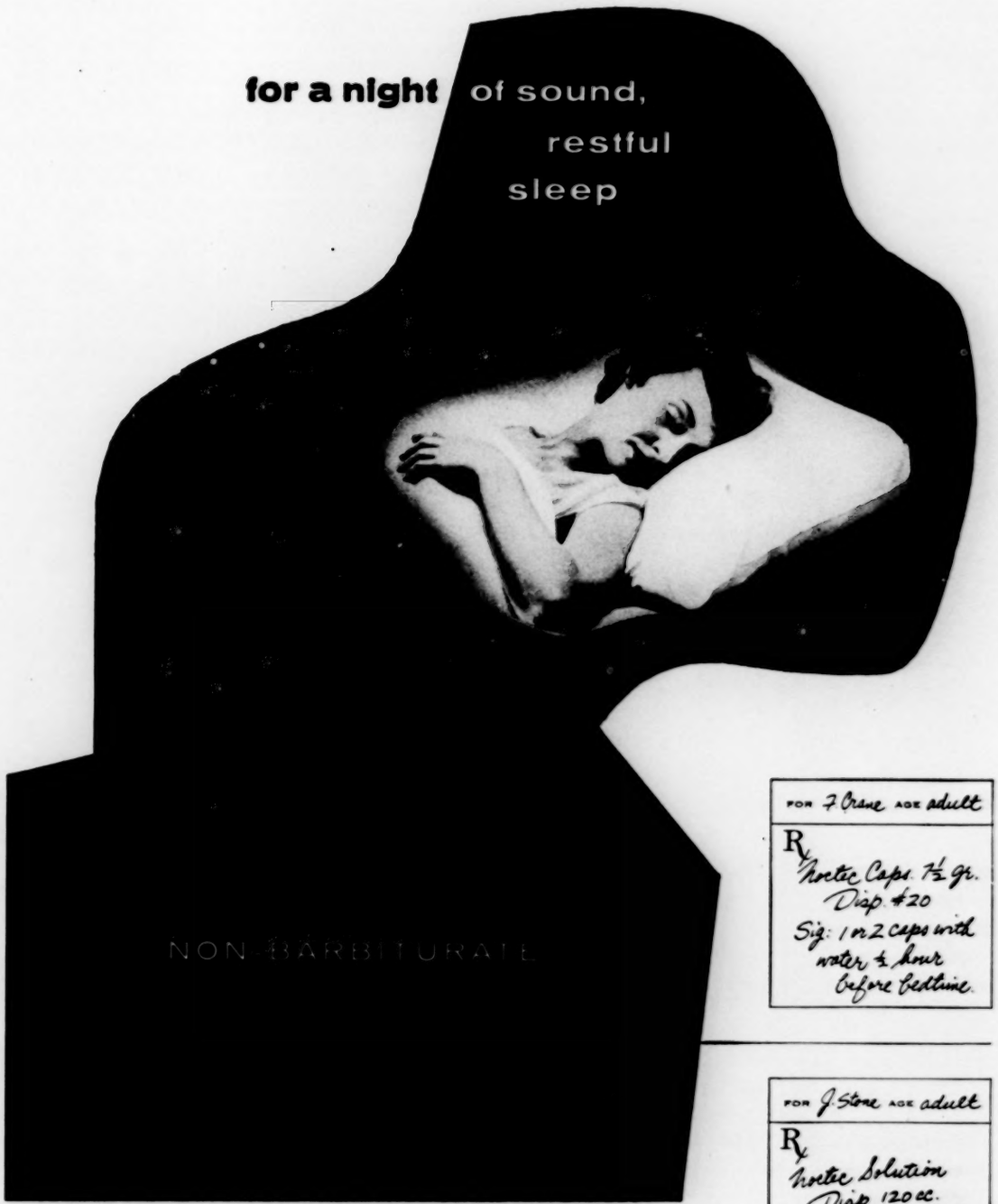
With two doses a day

Lipo Gantrisin 'Roche'—a new, palatable liquid for antibacterial therapy—offers three significant features:

1. Only two doses a day needed in most cases
2. Adequate twelve-hour blood levels after a single dose
3. Same therapeutic advantages as Gantrisin 'Roche'

Lipo Gantrisin® Acetyl—brand of acetyl sulfisoxazole in vegetable oil emulsion

for a night of sound,
restful
sleep



FOR J Crane AGE adult

℞ Noctec Caps. ½ gr.
Disp. #20
Sig: 1 or 2 caps with water ½ hour before bedtime.

FOR J. Stone AGE adult

℞ Noctec Solution
Disp 120 cc.
Sig: 1 tsp. in water or fruit juice ½ hour before bedtime

Squibb Quality—the Priceless Ingredient

SQUIBB

"NOCTEC"® IS A SQUIBB TRADEMARK

NOC-57

"...there is no diseased state in which the capillaries are not detrimentally modified..."[1]

Hesper-C

(HESPERIDIN COMPLEX AND ASCORBIC ACID)

to restore and maintain capillary integrity

A basic need in diverse disorders. Numerous studies have disclosed that capillary fragility is a basic pathological finding in many disease states.[2-8] The capillary-protective factors in Hesper-C act synergistically to *restore* and *maintain* capillary integrity.[3,9,10,11]

Normal capillary permeability helps limit or prevent hemorrhage and enhances utilization of essential tissue nutrients.

Indications: Capillary fragility associated with cardiovascular and cerebrovascular diseases, diabetes, hypertension, habitual abortion, arthritis, allergies, asthma, hematuria, inflammatory and edematous disorders.

Dosage: Initially, not less than 6 capsules or teaspoonsful daily. Maintenance dose, 4 capsules or teaspoonsful daily. Each capsule or teaspoonful (5 ml.) contains hesperidin complex 100 mg. and ascorbic acid 100 mg.

Supplied: *Capsules:* in bottles of 100 and 1000. *Liquid:* in bottles of 4 oz. and 12 oz.

References: **1.** Martin, G. J., et al.: Exper. Med. & Surg. *12*:535, 1954. **2.** Griffith, J. Q., Jr., and Lindauer, M. A.: Am. Heart J. *28*:758, 1944. **3.** Barishaw, S. B.: Exper. Med. & Surg.: *7*:358, 1949. **4.** Epstein, E. Z., and Greenspan, E. B.: Arch. Int. Med. *68*:1074, 1941. **5.** Warter, P. J., et al.: Delaware M. J. *20*:41, 1948. **6.** Beaser, S. B., et al.: Arch. Int. Med. *73*:18, 1944. **7.** Greenblatt, R. B.: Office Endocrinology, ed. 4, Springfield, Ill., Charles C Thomas, 1952. **8.** Gale, E. T., and Thewles, M. W.: Geriatrics *8*:80, 1953. **9.** Drezner, H. L., et al.: Am. Pract. & Digest. Treat. *6*:912, 1955. **10.** Selsman, G. J. V., and Horoschak, S.: Am. J. Digest Dis. *17*:92, 1950. **11.** Loughlin, W. C.: New York J. Med. *49*:1823, 1949.

Products of Original Research

NATIONAL

THE NATIONAL DRUG CO.
Philadelphia 44, Pa.

ANNOUNCING...

BIOPAR® FORTÉ

TABLETS

containing non-inhibitory intrinsic factor

providing **"parenteral B_{12} therapy" in a tablet**

2 tablets a day provide the same rapid and intense hemopoietic response as that obtained from injectable B_{12}

Biopar Forté, a new development in oral vitamin B_{12} therapy, contains non-inhibitory intrinsic factor superior to the ordinary factor preparations. The non-inhibitory factor permits optimal absorption of vitamin B_{12} at therapeutic dosage levels. Thus, stated potency and actual hemopoietic potency are more nearly equal than in vitamin B_{12} products containing the ordinary intrinsic factor.

Biopar Forté is also useful as an aid to nutrition, appetite, growth and convalescence; to correct deficient intestinal absorption of vitamin B_{12} particularly in elderly patients; and to relieve minor muscle and nerve pains, especially of neuritic origin.

Each Biopar Forté tablet contains:
Vitamin B_{12} with Intrinsic Factor Concentrate (non-inhibitory) ½ U.S.P. Unit (Oral)*
Vitamin B_{12} (activity equivalent) 25 mcg.

***Unitage established prior to compounding**

Supply: Bottles of 30 tablets

Attention: Store in a cool place

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY · KANKAKEE, ILLINOIS

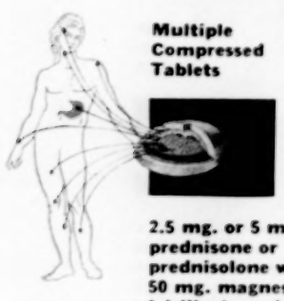
in rheumatoid arthritis

clinical evidence[1,2,3] indicates that to augment the therapeutic advantages of the "predni-steroids" antacids should be routinely co-administered to minimize gastric distress

ROUTINE CO-ADMINISTRATION MEANS

'Co-Hydeltra'

(Prednisolone Buffered)



Multiple Compressed Tablets

2.5 mg. or 5 mg. prednisone or prednisolone with 50 mg. magnesium trisilicate and 300 mg. aluminum hydroxide gel.

'Co-Deltra'

(Prednisone Buffered)

All the benefits of the "predni-steroids" plus positive antacid action to minimize gastric distress.

References: 1. Boland, E. W., *J.A.M.A.* **160**:613 (February 25) 1956. 2. Margolis, H. M. *et al.*, *J.A.M.A.* **158**:454 (June 11) 1955. 3. Bollet, A. J. *et al.*, *J.A.M.A.* **158**:459 (June 11) 1955.

MSD

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC.

PHILADELPHIA 1, PA.

'CO-DELTRA' *and* 'CO-HYDELTRA' *are trademarks of* MERCK & CO., INC.

Sigmamycin*

OLEANDOMYCIN TETRACYCLINE

added certainty in treatment of respiratory infections

new multi-spectrum synergistically strengthened antibiotic formulation

SIGMAMYCIN adds certainty in antibiotic therapy, particularly for the 90% of patients treated at home or in the office where sensitivity testing may not be practical, and provides: a new maximum in therapeutic effectiveness, a new maximum in protection against resistance, a new maximum in safety and toleration.

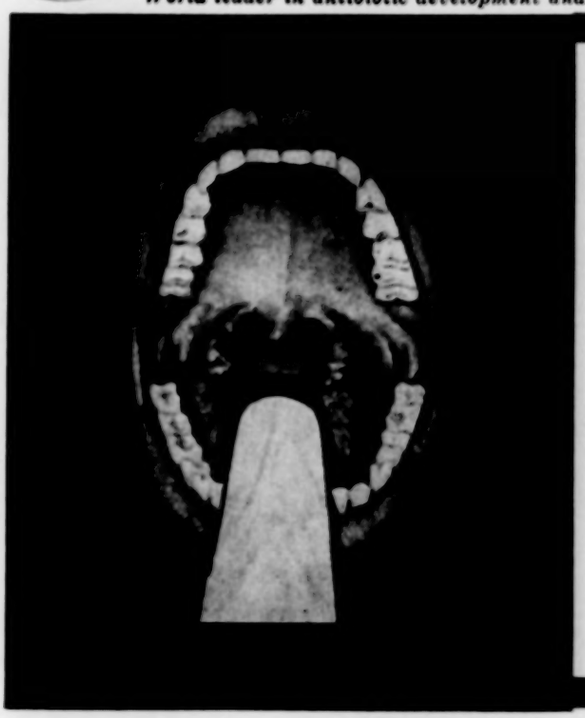
Supply: Capsules, 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.). Bottles of 16 and 100.

. . . and for a new maximum in palatability

New mint-flavored Sigmamycin for Oral Suspension, 1.5 Gm. in 2 oz. bottle; each 5 cc. teaspoonful contains 125 mg. (oleandomycin 42 mg., tetracycline 83 mg.). *Trademark

Pfizer

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.
World leader in antibiotic development and production



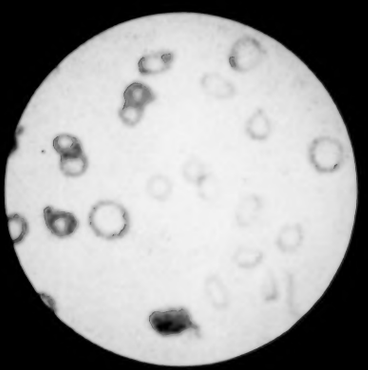
"...effective...in the treatment of a variety of infections seen regularly by the practicing clinician..." including pharyngitis, bronchitis and other respiratory infections

and "... often useful in the treatment of infections due to staphylococci resistant to one or several of the regularly used antibiotics"

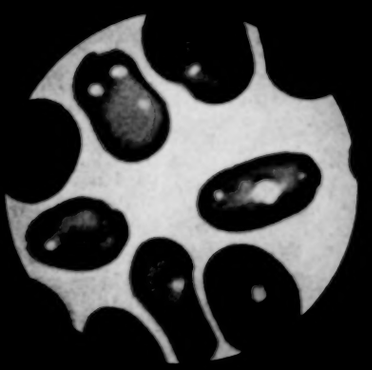
"side effects . . . [are] notable by their absence"[1]

1. Carter, C. H., and Maley, M. C.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 51.

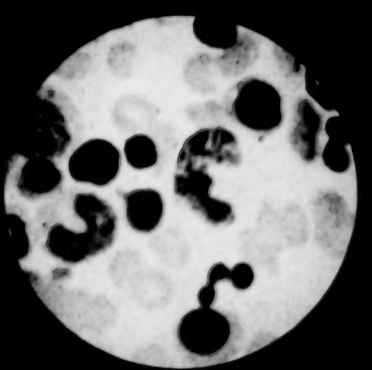
MICROCYTIC
HYPOCHROMIC ANEMIA



MACROCYTIC ANEMIA



PERNICIOUS ANEMIA



decide

WHEN MORE THAN A HEMATINIC IS REQUIRED, HEPTUNA PLUS supplies iron, vitamins and trace minerals. The formula, liberal in iron, folic acid and B_{12} content, will correct most microcytic anemias, of course. But more than that, HEPTUNA PLUS is widely useful in the commonest anemia of all: anemia complicated by other nutritional deficiencies.

In moderate conditions, 1 to 3 capsules daily. In severe cases, 4 or more daily. Supplied: Bottles of 100 soft, soluble capsules.

HEPTUNA® PLUS

FOR ALL TREATABLE ANEMIAS, ROETINIC is formulated with the new intrinsic factor/B_{12} concentrate and high folic and ascorbic acids content. Aimed primarily at the more complicated macrocytic anemias of faulty hemopoiesis and those normocytic anemias due to hemolysis.

Therapeutic dosage is just one capsule daily. Supplied: Bottles of 30 and 100 soft, soluble capsules.

ROETINIC®

FOR THE ANEMIAS OF PREGNANCY, OBRON HEMATINIC is a complete hematinic and prenatal supplement. Formula includes high iron content plus calcium, folic acid, B_{12}, eight other minerals, eight essential vitamins.

Dosage as required, usually two capsules daily. Supplied: Bottles of 100 soft, soluble capsules.

OBRON® HEMATINIC

ROERIG

CHICAGO 11, ILLINOIS PEACE of mind ATARAX®

INCREMIN

LYSINE-VITAMIN SUPPLEMENT LEDERLE

Specify INCREMIN TABLETS to stimulate appetite in your problem-eater, underweight, or generally below-par patients of all ages.

INCREMIN TABLETS are highly palatable, caramel flavored. May be orally dissolved, chewed, or swallowed. Dosage only 1 tablet daily.

Each INCREMIN TABLET *contains:*

l-Lysine	300 mg.
Vitamin B_{12}	25 mcgm.
Thiamine (B_1)	10 mg.
Pyridoxine (B_6)	5 mg.

(INCREMIN Drops contain 1% alcohol)

Remember INCREMIN DROPS. Same formula. Cherry flavor. Can be mixed with milk, milk formula, or other liquid. In 15 cc. polyethylene dropper bottle. *Dosage:* 0.5 to 1 cc. (10-20 drops) daily.

Lederle

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, N. Y.

*Reg. U. S. Pat. Off.

OR CHANGE

without recalculation of dosage

VARICK Pharmaceutical Company Inc

Back Issues Wanted

(MUST BE IN GOOD CONDITION)

THE AMERICAN JOURNAL OF MEDICINE

will pay $1.00 per copy for the following issues:

January 1948
March 1948
July 1948
August 1951
February 1953
December 1954
May 1955
August 1955
September 1955
October 1955

Send to

The American Journal of Medicine, Inc.
49 West 45th Street New York 36, N. Y.

ELDEC

Kapseals®

comprehensive physiologic supplement

each Kapseal contains:

VITAMINS	
Vitamin A	1,667 Units (0.5 mg.)
Vitamin B_1 mononitrate	0.67 mg.
Ascorbic acid	33.3 mg.
Nicotinamide	16.7 mg.
Vitamin B_2	0.67 mg.
Vitamin B_6	0.5 mg.
Vitamin B_{12} with intrinsic factor concentrate	0.033 USP Unit (oral)
Folic acid	0.1 mg.
Choline bitartrate	6.67 mg.
Pantothenic acid (as the sodium salt)	5 mg.
MINERALS	
Ferrous sulfate (exsiccated)	16.7 mg.
Iodine (as potassium iodide)	0.05 mg.
Calcium carbonate	66.7 mg.
DIGESTIVE ENZYMES	
Taka-Diastase®	20 mg.
Pancreatin	133.3 mg.
PROTEIN IMPROVEMENT FACTORS	
l-Lysine monohydrochloride	66.7 mg.
dl-Methionine	16.7 mg.
GONADAL HORMONES	
Methyl testosterone	1.67 mg.
Theelin	0.167 mg.

DOSAGE:

One Kapseal three times daily before meals. Female patients should follow each 21-day course with a 7-day rest interval.

PACKAGING:

ELDEC Kapseals are available in bottles of 100.

00003

combating the
aging complex
now

promotes vigor
and vitality
later

ELDEC*

Kapseals®

mineral-vitamin-hormone supplement

favorably alters concomitants of aging

- vitamins and minerals
  to help maintain cellular function
- enzymes to aid digestion
- amino acids to help maintain nitrogen balance
- steroids to stimulate anabolism

*TRADE-MARK

50083

MEDICAMENTA VERA

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

recognized

as a potent, specific anti-arthritic

established

by over 100 million patient days

substantiated

in more than 700 published reports

BUTAZOLIDIN®

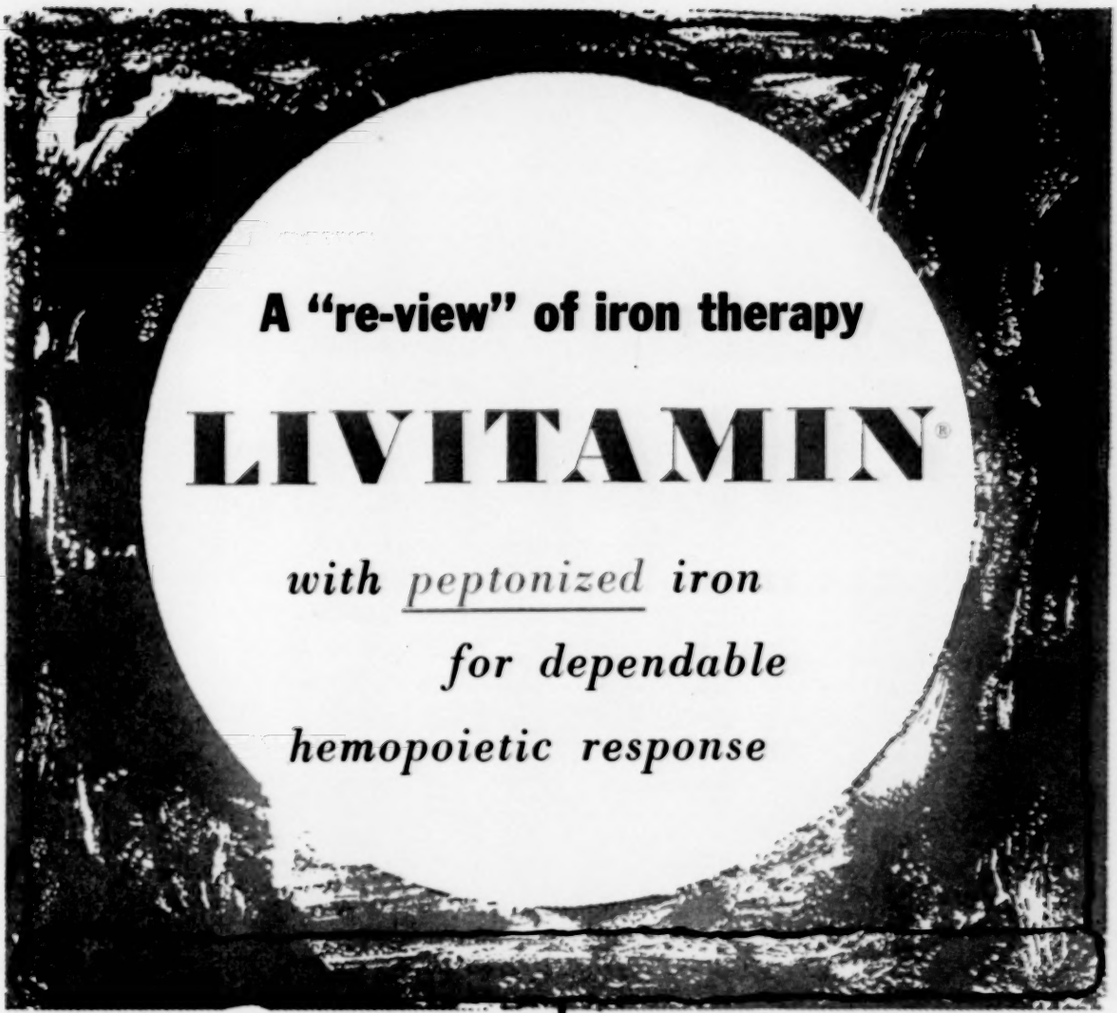
(phenylbutazone GEIGY)

potent, specific anti-arthritic

Based on an impressive background of achievement attained over a period of four years involving both long-term and short-term therapy in all the major forms of arthritis, BUTAZOLIDIN is recognized as one of the most effective anti-arthritic agents currently available.

relieves pain
improves function
resolves inflammation

GEIGY



It is well-established that peptonized iron is virtually predigested. Anemias refractory to other forms of iron will often respond promptly to Livitamin. And the Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

Current studies* show Peptonized Iron

—One-third as toxic as ferrous sulfate.
—Absorbed as well as ferrous sulfate.
—Non-astringent.
—Free from tendencies to disturb digestion. (One-tenth as irritating to the gastric mucosa as ferrous sulfate.)
—Highly effective in iron-deficiency anemias.

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate. Read before the American Association for the Advancement of Science, Atlanta, Georgia, December, 1955

EACH FLUIDOUNCE CONTAINS:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	0.42 Gm.
Manganese citrate, soluble	0.158 Gm.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Cobalamin Conc. (Vitamin B_{12} activity)	20 mcg.
Niacinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

The S. E. MASSENGILL Company

Bristol, Tennessee

New York Kansas City San Francisco

Rauwiloid®

A Better Antihypertensive

. . . because among all Rauwolfia preparations Rauwiloid (alseroxylon) is maximally effective and maximally safe . . . because least dosage adjustment is necessary . . . because the incidence of depression is less . . . because up to 80% of patients with mild labile hypertension and many with more severe forms respond to Rauwiloid alone.

A Better Tranquilizer, too

. . . because Rauwiloid's *nonsoporific* sedative action relieves anxiety in a long list of unrelated diseases not necessarily associated with hypertension . . . without masking of symptoms . . . without impairing intellectual or psychomotor efficiency.

Dosage: Simply two 2 mg. tablets at bedtime. After full effect one tablet suffices.

Best first step when more potent drugs are needed

Rauwiloid is recognized as basal medication in all grades and types of hypertension. In combination with more potent agents it proves synergistic or potentiating, making smaller dosage effective and freer from side actions.

Rauwiloid® + Veriloid®

In moderate to severe hypertension this single-tablet combination permits long-term therapy with dependably stable response. Each tablet contains 1 mg. Rauwiloid and 3 mg. Veriloid. Initial dose, 1 tablet t.i.d., p.c.

Rauwiloid® + Hexamethonium

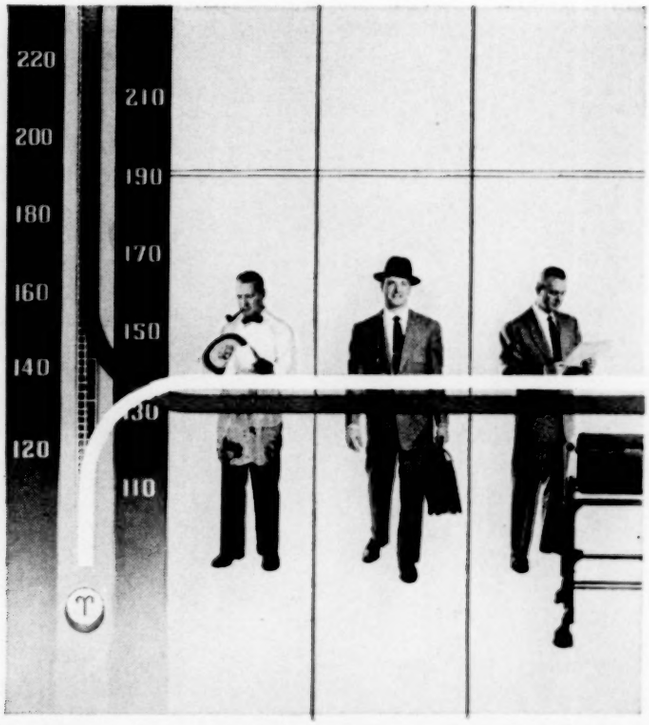
In severe, otherwise intractable hypertension this single-tablet combination provides smoother, less erratic response to hexamethonium. Each tablet contains 1 mg. Rauwiloid and 250 mg. hexamethonium chloride dihydrate. Initial dose, ½ tablet q.i.d.

Riker LOS ANGELES

Diamox

Lederle

tangible
relief
in
premenstrual
tension



Predictable hypotensive effect—orally

MECAMYLAMINE HYDROCHLORIDE

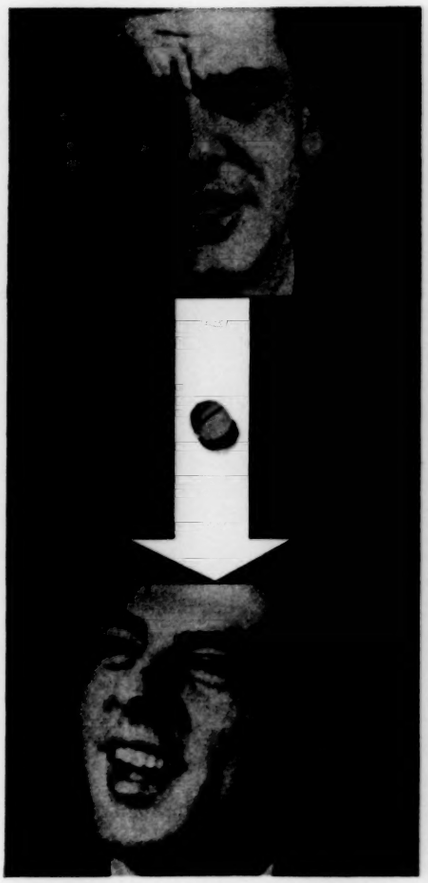
INVERSINE—a secondary amine, different from all other ganglionic blocking agents—has many clinical advantages: **1.** Gives reproducible effects. **2.** Is most potent of all oral ganglionic blockers. **3.** Provides smooth and predictable response. **4.** Is completely absorbed. **5.** Onset of action is gradual. **6.** Small oral dose gives desired hypotensive effect. **7.** Is effective even in patients refractory to other ganglionic blockers.

Dosage: Initial dose, 2.5 mg. twice daily, increased by 2.5 mg. at 2-day intervals. Average daily dose 25-30 mg.
Supplied: 2.5 mg. scored tablets and 10 mg. quarter-sected tablets in bottles of 100.

INVERSINE IS A TRADEMARK OF MERCK & CO., INC.,

MSD

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.



announcing

Cantil
for the colon

ulcerative colitis • irritable colon • mucous colitis • spastic colitis • diverticulitis, diverticulosis • rectospasm • diarrhea following G.I. surgery • bacillary and parasitic disorders

EFFECTIVE

relieves pain, cramps, diarrhea
helps restore normal tone and motility

SELECTIVE

avoids widespread autonomic disturbance
unusually free of "antispasmodic" side effects, urinary retention

HOW CANTIL IS PRESCRIBED

One or two tablets three times a day preferably with meals and one or two tablets at bedtime.

CANTIL—TWO FORMS

CANTIL (plain)—25 mg. of CANTIL in each scored tablet—bottles of 100.

CANTIL with Phenobarbital—25 mg. of CANTIL and 16 mg. of phenobarbital (Warning: May be habit forming.) in each scored tablet—bottles of 100.

CANTIL is the *only* brand of N-methyl-3-piperidyl-diphenylglycolate methobromide.

For more detailed information, request Brochure No. NDA 16, Lakeside Laboratories, Milwaukee 1, Wisconsin.

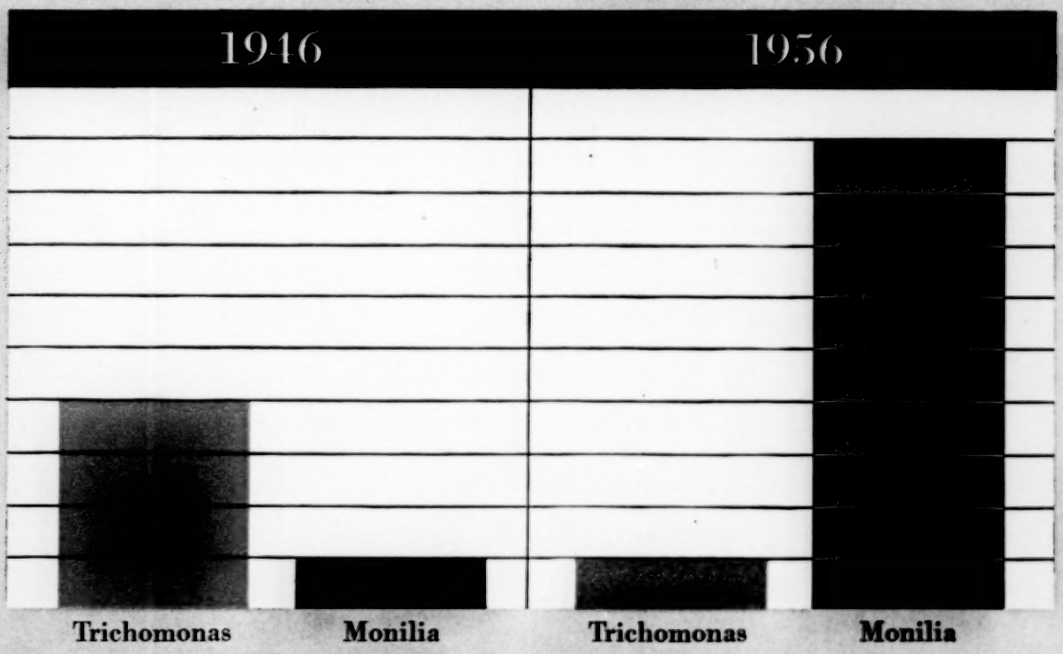
LAKESIDE

08756

AN IMPORTANT CLINICAL CONSIDERATION:

the rising incidence of moniliasis since the introduction of broad spectrum antibiotics

EXAMPLE: Candida albicans (monilia) as a cause of vaginitis[1,2]



The use of *any* antibiotic may cause the troublesome and potentially serious complication of monilial superinfection by suppressing the bacterial flora of the intestinal tract and allowing monilia to proliferate.

"Even one day of therapy may be sufficient to provoke an unfavorable chain of events and this fact should be kept in mind whenever a patient is to receive an oral antibiotic for even a minimal period of time."[3]

MYSTECLIN IS PARTICULARLY INDICATED IN:

the only broad spectrum antibiotic preparation with added protection against monilial superinfection

Mysteclin

each dose is fresh

... for complete potency

FOLBESYN*

VITAMINS LEDERLE

B COMPLEX + C

Separate packaging of dry vitamins and diluent (mixed immediately before injection) assure controlled dosage. The folic acid solution is specially prepared to preserve full potency and to serve for quick solution of the dried vitamins. FOLBESYN may be conveniently added to standard intravenous solutions.

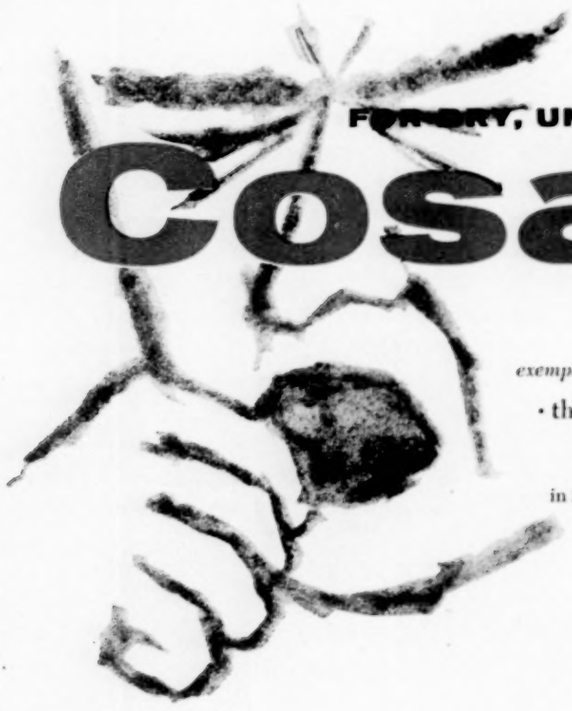
Dosage: 2 cc. daily.

Each 2 cc. dose contains:

Thiamine HCl (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	50 mg.
Pyridoxine HCl (B_6)	5 mg.
Sodium Pantothenate	10 mg.
Ascorbic Acid (C)	300 mg.
Folic Acid	3 mg.
Vitamin B_{12}	15 mcgm.

Lederle LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, N. Y.

*REG. U. S. PAT. OFF.



FOR DRY, UNPRODUCTIVE COUGH

Cosanyl®

exempt narcotic—contains dihydrocodeinone bitartrate

- the original syrup cocillana compound
- delicious peach-like flavor

in 2-ounce, 4-ounce, 16-ounce, and 1-gallon bottles

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

NOW—EFFECTIVE STEROID HORMONE THERAPY OF RHEUMATIC AFFECTIONS WITH GREATER SAFETY AND ECONOMY

PABALATE-HC

Robins

Pabalate with Hydrocortisone

Clinical evidence indicates that, in Pabalate-HC, the synergistic antirheumatoid effects of hydrocortisone, salicylate, para-aminobenzoate, and ascorbic acid achieve satisfactory remission of symptoms in *up to 85% of cases studied*

—*with a much higher degree of safety*

—*even when therapy is maintained for long periods*

—*at significant economy for the patient*

FORMULA

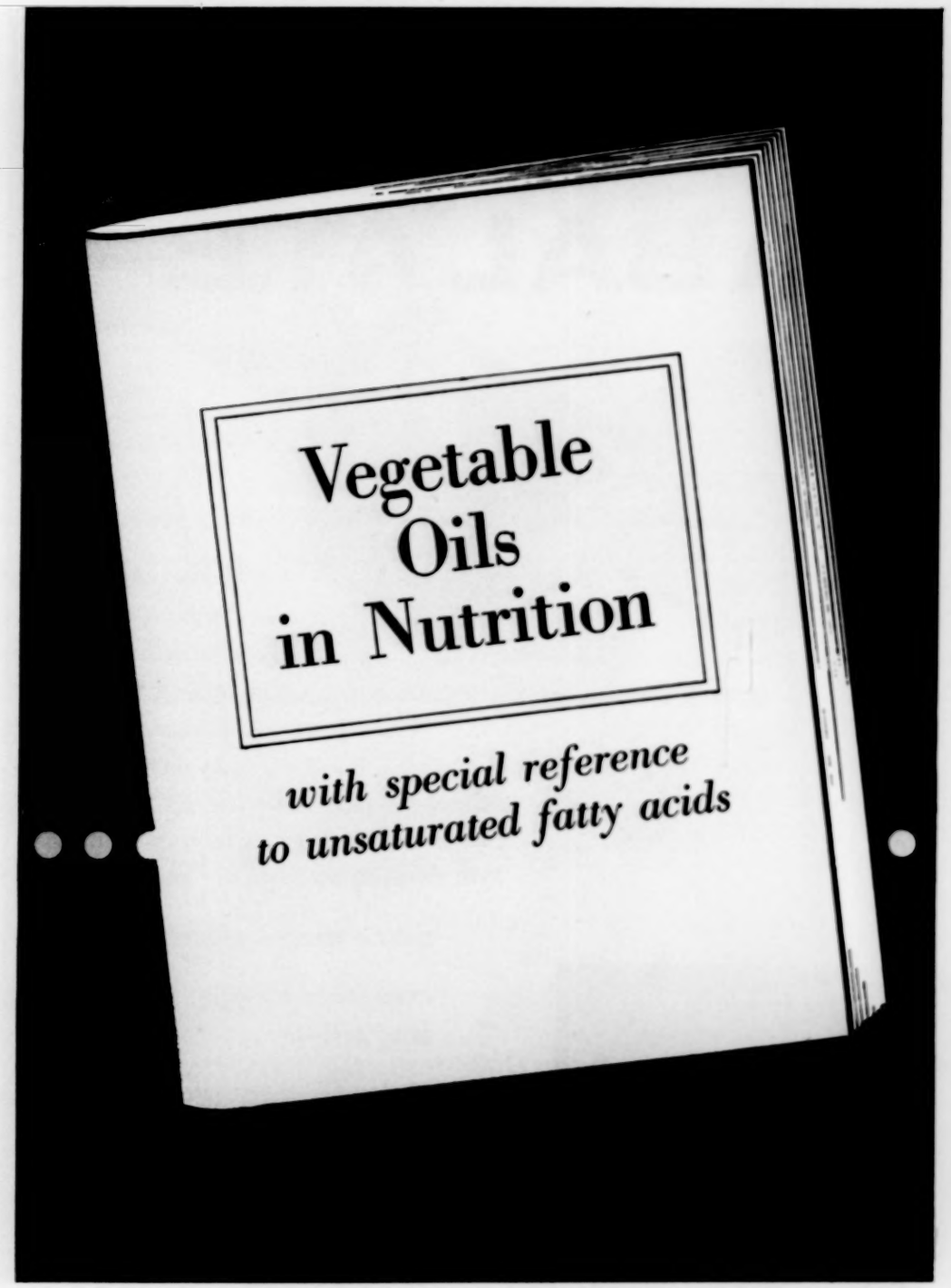
Each tablet of Pabalate-HC contains 2.5 mg. of hydrocortisone—50% more potent than cortisone, yet not more toxic.

AVAILABLE FOR YOUR PRESCRIPTION NOW

A. H. ROBINS CO., INC. RICHMOND 20, VIRGINIA

Ethical Pharmaceuticals of Merit since 1878

Now available... a new manual



. . . "Vegetable Oils in Nutrition"

Timely, Comprehensive, Useful . . . with special reference to unsaturated fatty acids

TIMELY . . . a summary of the literature in this important field

COMPREHENSIVE . . . a review of authoritative experimental and clinical research pertaining to the special metabolic roles of polyunsaturated fats

USEFUL . . . in a form suitable for continual reference use. *Valuable to clinician, nutritionist, chemist.* Bibliography listing all pertinent publications

The role of dietary lipids in health and disease is universally assuming new importance. Evidence is accumulating that quality of the dietary fat may be more important than quantity.

This review provides a broad perspective on current authoritative and clinical opinions regarding the relative dietary characteristics of saturated and unsaturated fats . . . and the indispensable nutritional role of polyunsaturated fatty acids.

Mazola is a vegetable oil (not hydrogenated) made from corn. It is unsaturated . . . a prime source of essential linoleic acid.

Corn Products Refining Company, the manufacturer of Mazola corn oil, will keep you informed of significant new developments in this rapidly expanding field.

ORDER YOUR COPY NOW . . .

Medical Department
Corn Products Refining Co.
17 Battery Place, New York 4, New York

Please send me, postpaid, the new reference manual and monograph on "Vegetable Oils in Nutrition."

Name_____

Address_____

City_____ State_____

IN DIABETES...

greater security against vascular complications

Increased threat of vascular complications in diabetic patients can result from recurring episodes of inadequate control; at such times amino acids are "wasted" by de-amination in the liver and normal dietary security against lipotropic deficiency fades.

TRADE MARK

Gericaps

(Sherman Lipotropic Capsule) **One capsule t.i.d.**

Gericaps contain the true lipotropics, choline and inositol, which are unaffected by de-amination in the liver. Three capsules daily provide the equivalent of 3 Gm. choline dihydrogen citrate.

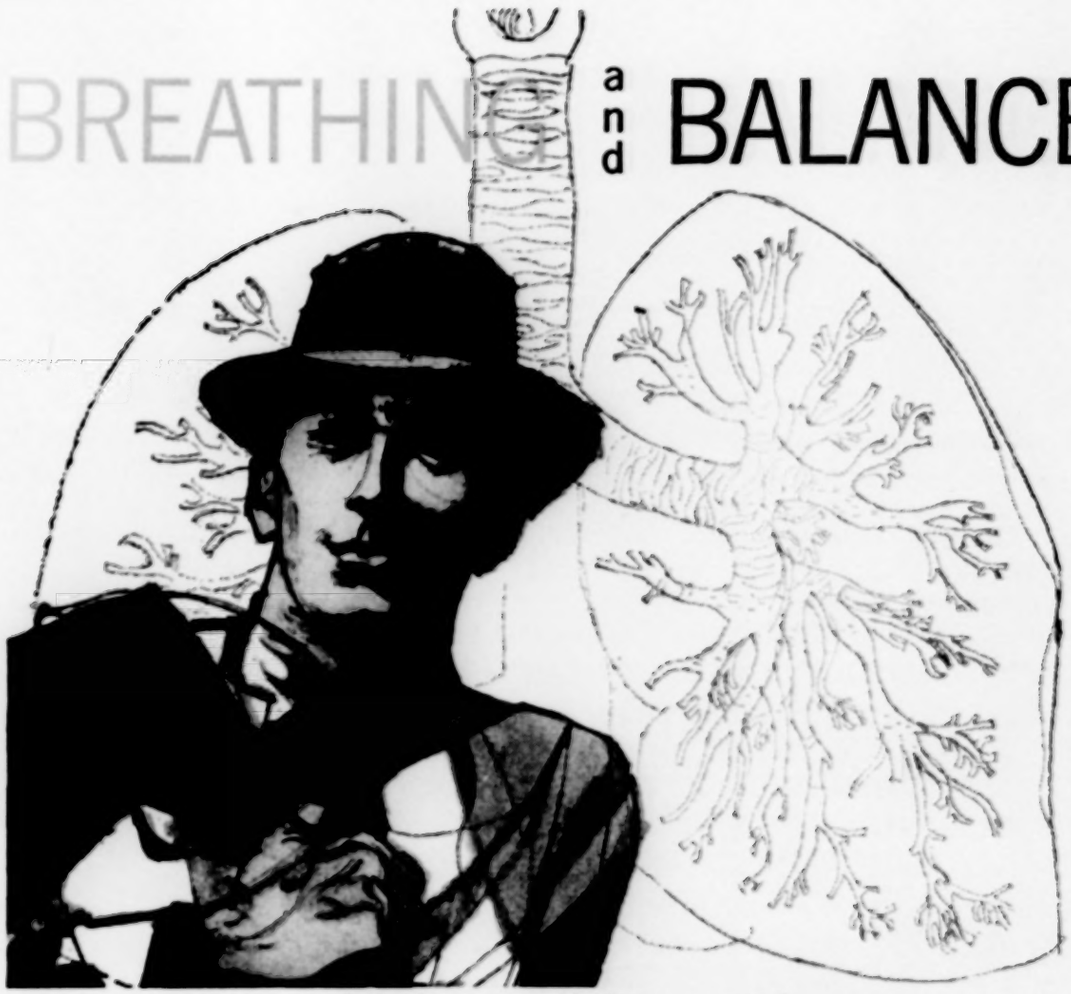
This dose also provides 60 mg. rutin and 37.5 mg. ascorbic acid to maintain or improve capillary integrity, as well as 3000 units vitamin A, 3 mg. thiamine hydrochloride, 3 mg. riboflavin, 12 mg. niacinamide, 0.75 mg. pyridoxine hydrochloride, and 3 mg. calcium pantothenate.

SEND FOR comprehensive review:

"Prevention of Vascular Complications of Diabetes"

SHERMAN LABORATORIES
BIOLOGICALS • PHARMACEUTICALS

BREATHING and BALANCE



in bronchial asthma

Sterane®

brand of prednisolone

whenever corticosteroids are indicated

provides restoration of breathing capacity — Relief of symptoms [bronchospasm, cough, wheezing, dyspnea] is maintained for long periods with relatively small doses.*

minimal effect on electrolyte balance — "in therapeutically effective doses . . . there is usually no sodium or fluid retention or potassium loss."* Lack of edema and undesirable weight gain permits more effective therapy particularly for those with cardiac complications.

Supplied: White, 5 mg. oral tablets, bottles of 20 and 100. Pink, 1 mg. oral tablets, bottles of 100. Both are deep-scored.

*Schwartz, E.: New York J. Med. 56:570, 1956.

PFIZER LABORATORIES, Brooklyn 6, New York
Division, Chas. Pfizer & Co., Inc.

SYMPTOMATIC

RELIEF... PLUS!

ACHROCIDIN*

TETRACYCLINE-ANTIHISTAMINE-ANALGESIC COMPOUND

Tablets and Syrup

ACHROCIDIN is particularly valuable in treating acute respiratory infections during epidemics or when questionable middle ear, pulmonary, nephritic, or rheumatic signs are present.

ACHROCIDIN offers early, potent therapy against such disabling complications as otitis media, sinusitis, bronchitis to which the patient may be highly vulnerable at this time.

Included in the comprehensive ACHROCIDIN formulation are the analgesic components recommended for prompt relief of common cold symptoms.

Adult dosage for ACHROCIDIN Tablets and new, caffeine-free ACHROCIDIN Syrup is two tablets or teaspoonfuls of syrup three or four times daily. Dosage for children according to weight and age.

Available on Prescription Only

Each tablet contains:

ACHROMYCIN® Tetracycline	125 mg.	Caffeine	30 mg.
Phenacetin	120 mg.	Salicylamide	150 mg.
		Chlorothen Citrate	25 mg.

Lederle

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

*Trademark

. . . for the patient with seborrheic dermatitis of the scalp

SELSUN®

Pleasant, simple-to-use Selsun brings quick, welcome relief to scalp-sufferers. The first few applications control itching, burning symptoms. And Selsun stops scaling in 81-87% of seborrheic dermatitis, 92-95% of all common dandruff cases.

Then each Selsun application keeps the scalp healthy up to four weeks. Directions accompany each 4-fluidounce plastic bottle of Selsun. Sold only on physician's prescription.

Abbott

701001

®*Selenium Sulfide, Abbott*

NUDGES YOUR PATIENT TO SLEEP

No abrupt onset with Placidyl: sleep comes gently, imperceptibly. Worries of the day vanish . . . the mind stops its busy spinning . . . and within the hour your patient is sleeping like a kitten. *Non*barbiturate.

100-mg., 200-mg., and 500-mg. capsules, bottles of 100 Abbott

Do you want the literature? Write to Professional Services, Abbott Laboratories, North Chicago, Illinois

701002

NOW AVAILABLE FOR
DAYTIME TRANQUILIZATION
AND SEDATION

Placidyl

100-mg. and 200-mg. capsules

Q. *In what ways can I use these new sizes of Placidyl?*
A. With them you can now produce any degree of effect from tranquilization, through sedation, to hypnosis.

Q. *What are the indications?*
A. Placidyl is indicated in cases of nervous or muscular tension, mild anxiety or excitement, and in simple insomnia resulting from these conditions.

Q. *Does Placidyl provide muscle relaxation?*
A. Yes, it possesses mild muscle relaxant properties which provide added advantage in tension states.

Q. *Does Placidyl sedation hinder the patient's work?*
A. No. Investigators have agreed that by selecting a suitable dose, tranquilization can be achieved without any confusion or loss of contact with surroundings.

Q. *What daytime dosage is recommended?*
A. Adult dose ranges from 100 mg., b.i.d., to 200 mg., t.i.d., depending on patient's condition and response.

Q. *Are the new dosage sizes useful for insomnia, too?*
A. Yes. 500 mg. remains the average hypnotic dose; but if your patient also is taking Placidyl by day, 100 or 200 mg. at bedtime is usually enough to stop insomnia.

Q. *Is Placidyl sold under other trade names?*
A. No. It is a mild, halogenated carbinol, structurally unique, made only by Abbott. Supplied in 100-mg., 200-mg., and 500-mg. capsules, bottles of 100. Abbott

7020A7

66th YEAR OF PUBLICATION

The Leading Independent Surgical Journal

PRESENTS THE PAPERS OF . . .

The American Association
for the Surgery of Trauma

•

The Pacific Coast Surgical Association

•

The American Society of Maxillofacial Surgeons

•

OTHER REGULAR FEATURES . . .

Modern Operative Technics
Practical Surgical Suggestions

START YOUR SUBSCRIPTION WITH THIS ISSUE

The American Journal of Surgery
49 West 45th St., New York 36, N. Y.
Please enter my subscription to The American Journal of Surgery. Yearly $15.00 U.S.A.—$16.00 Canada—$17 Foreign

Name.....

Address .....

City.....Zone.....State.....

Your R_x of **Sustagen Feedings q.2h.**

buffers acid
builds tissue
accelerates healing
provides a bland high protein diet

Sustagen®

PROVIDES FOOD FOR THE PATIENT
PROVIDES THERAPY FOR THE LESION

a peptic ulcer patient ...

comfortable...well fed...**on the job!**

MEAD JOHNSON

SYMBOL OF SERVICE IN MEDICINE

prescribe RAUDIXIN to break the
mental tension—hypertension cycle

RAUDIXIN

NOW AVAILABLE!

flexin

(Zoxazolamine,* McNeil)

engestic® coated (ENTERIC)

PROMPT RELIEF IN LOW BACK PAIN

With FLEXIN, "...17 of the 20 patients with post-traumatic muscle spasm of the low back had excellent or good responses."[1]

AVAILABLE: Tablets, Engestic Coated, pink, 250 mg., bottles of 36.
Tablets, scored, yellow, 250 mg., bottles of 50.

1. Wallace, S. L.: Zoxazolamine (Flexin) in Low Back Disorders, to be published.

*U.S. Patent Pending

08057

McNEIL

relaxes
both mind
and
muscle

for the average patient in everyday practice

- well suited for prolonged therapy
- well tolerated, nonaddictive, essentially nontoxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to chlorpromazine or reserpine
- does not produce significant depression
- orally effective within 30 minutes for a period of 6 hours

Indications: **anxiety and tension states, muscle spasm.**

THE ORIGINAL MEPROBAMATE®

Miltown®

Tranquilizer with muscle-relaxant action

DISCOVERED AND INTRODUCED

BY WALLACE LABORATORIES, *New Brunswick, N.J.*

2-methyl-2-n-propyl-1,3-propanediol dicarbamate—U.S. Patent 2,724,720

SUPPLIED: *400 mg. scored tablets. Usual dose: 1 or 2 tablets t.i.d.*

Literature and Samples Available on Request

THE MILTOWN MOLECULE

CM-3707-R2

NOW—the unequalled advantages of K_1—orally

Tablets

MEPHYTON®

(VITAMIN K_1, MERCK)

". . . vitamin K_1 is more effective than any other agent now available in combating drug-induced hypoprothrombinemia."[1] "Vitamin K_1 appears to be equally effective by the oral or intravenous route."[2] Beneficial effects are apparent in 6 to 10 hours following oral use.

Supplied: Oral **MEPHYTON**—tablets of 5 mg. of vitamin K_1, in bottles of 100. Emulsion of **MEPHYTON**—in boxes of six 1-cc. ampuls, 50 mg. of K_1 per cc.

References: 1. Gamble, J.R., et al. Arch. Int. Med. **95**:52, 1955. 2. Gamble, J.R., et al. J. Lab. & Clin. Med. **42**:805, 1953.

MSD

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC. PHILADELPHIA 1, PA.

when infection strikes the respiratory tract . . .

ILOTYCIN

(Erythromycin, Lilly)

provides singularly effective antibiotic therapy, because

- Virtually all gram-positive organisms are inherently sensitive
- Allergic reactions following systemic therapy are rare
- Bactericidal action kills susceptible organisms
- Normal bacterial flora of the intestine is not appreciably disturbed

The usual adult dose is 250 mg. every six hours.

***Available** in specially coated tablets, pediatric suspension, drops, ointments, and I.V. ampoules.*

732024

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

The American Journal of Medicine

VOL. XXII FEBRUARY, 1957 No. 2

Editorial

The Sympathetic Nervous System, the Vascular Volume and the Venous Return in Relation to Cardiovascular Integration

THE effect of the sympathetic nervous system on the circulation has long been a subject for investigation. In the past, most emphasis was placed on the role of this system in the regulation of arteriolar tone. This is its most obvious effect but recent studies have also emphasized the importance of the sympathetic system in adjusting the total vascular volume and, hence, venous return and cardiac output. In these experiments norepinephrine, which mimics sympathetic vasoconstriction, and hexamethonium, which produces sympathetic inhibition, were employed as pharmacologic tools.

The pertinent experiments were as follows: A pump, with output which remained constant under marked variations in peripheral resistance, was substituted for the left ventricle in a dog.[1] The pulmonary drainage of blood was carried to a reservoir by means of a plastic tube inserted into the left auricle. The blood was pumped from the reservoir through a T-tube in the descending thoracic aorta. The right ventricle was left undisturbed. This preparation maintained normal intravascular pressures with an output regulated between 2 and 3 liters per minute. If the animal was not disturbed the reservoir level remained constant, showing that the right ventricular output was keeping pace with the "left" or pump output.

If norepinephrine (which simulates sympathetic vasoconstriction in "physiologic" dosages) was injected into the animal there was not only an increase in vascular pressures but also an increase in the amount of blood in the reservoir. During the action of the drug the animal lost to the reservoir approximately 200 to 300 ml. of circulating blood volume, approximately one-fifth of the total blood volume in the dog. When hexamethonium was injected instead of norepinephrine the pressures fell throughout the vascular system and the animal took up 200 to 300 ml. of blood volume from the reservoir.[2]

It is obvious that following norepinephrine the total vascular volume of the animal decreased approximately one-fifth in order for the excess blood to be "squeezed out" into the reservoir. When the sympathetic impulses were inhibited following administration of the ganglionic blocking agent vascular volume in the animal increased by a similar amount. These changes in vascular capacity were too large to be explained on the basis of arteriolar constriction alone, but must have included postarteriolar vessels as well, that is, capillaries and/or venules and veins. Simultaneous with the rise in pressures following the injection of norepinephrine there was an increase in left auricular drainage and pulmonary arterial pressure reflecting an increase in right ventricular output. It is axiomatic that the right ventricle cannot pump more blood than is delivered to it. Hence, in order to increase its output in the face of a constant output (pump) from the left side, the right

[1] ROSE, J. C., BROIDA, H. P., HUFNAGEL, C. A., GILLESPIE, J. F., RABILE, P. J. and FREIS, E. D. A method for the study of the circulation in the dog using a mechanical left ventricle. *J. Appl. Physiol.*, 7: 580, 1955.

[2] ROSE, J. C. and FREIS, E. D. The effects of norepinephrine and hexamethonium on the total vascular volume in the dog. In preparation.

ventricle must have received an increased venous return. This, in turn, was due to the sudden decrease in vascular volume.

These studies demonstrate that sympathetic stimulation produces an integrated response. By decreasing vascular volume, more blood enters the right heart, providing for an increased cardiac output. With sympathetic "blockade," the opposite effects occurred; there was a fall in right ventricular output, systemic venous pressures and pulmonary arterial pressures, reflecting a decrease in venous return.

Further work has confirmed and extended these findings in man.[3] When hexamethonium was given to hypertensive patients, who were not in heart failure, the arterial pressure fell, and with it there was a commensurate reduction in cardiac output. The pressures in the right auricle, right ventricle and pulmonary artery also decreased, indicating that the reduced output was secondary to a failure of venous return. In the light of the observations in the dog it seems reasonable to conclude that an increase in peripheral vascular volume accounted for the failure of venous return.

The exquisite regulation of vascular volume by the sympathetic nervous system under normal conditions was demonstrated in a simple experiment.[4] The sympathetic vasoconstrictor reflexes were inhibited with hexamethonium in a group of normotensive or hypertensive subjects. Sufficient time was permitted to elapse for stabilization of blood pressure. A phlebotomy then was carried out, following which the blood was reinfused under pressure. With each 50 ml. of blood removed during the bleeding there was a perceptible decline of blood pressure. After removal of only 350 to 500 ml. of blood the arterial pressure had fallen by decrements to collapse levels. During reinfusion the blood pressure rose stepwise with each increment of blood replaced and, when completely reinfused, the level of arterial pressure also had returned to the preinfusion level.

[3] Freis, E. D., Rose, J. C., Partenope, E. A., Higgins, T. F., Kelley, R. T., Schnaper, H. W. and Johnson, R. L. The hemodynamic effects of hypotensive drugs in man. III. Hexamethonium. *J. Clin. Investigation*, 32: 1285, 1953.

[4] Freis, E. D., Stanton, J. R., Finnerty, F. A., Jr., Schnaper, H. W., Johnson, R. L., Rath, C. E. and Wilkins, R. W. The collapse produced by venous congestion of the extremities or by venesection following certain hypotensive agents. *J. Clin. Investigation*, 30: 435, 1951.

Inhibition of the sympathetic vasoconstrictor reflexes apparently had converted the vasculature into a static system. In this system venous return, cardiac output and, hence, arterial pressure were dependent directly on the effective circulating blood volume. Withdrawals of 50 cc. of blood, or less than 1 per cent of the total blood volume, affected venous return significantly, and removal of less than 10 per cent produced collapse. In the presence of an uninhibited sympathetic nervous system, therefore, minor reductions of effective circulating blood volume (1 per cent or less) activate the baroreceptor reflexes. These reflexes then reduce the vascular capacity by the precise amount required to restore the venous return and cardiac output to the level existing prior to the blood loss.

Effective circulating blood volume may be reduced by means other than hemorrhage. For example, during quiet standing more than 500 ml. excess blood may accumulate in the lower extremities. In the presence of ganglionic "blockade" postural hypotension will result, due to failure of venous return. Measurements of the amount trapped out indicated that postural hypotension induced by drugs occurs not so much because of excessive pooling of blood in the lower extremities but chiefly because of failure of compensatory reduction in vascular volume throughout the body.[4]

Clinical Implications. It has long been known that counterpressure, such as immersion of the lower body in water or application of pressure bandages or pressure suits, will counteract postural hypotension. In this case a reduction in peripheral vascular volume is accomplished by external pressure. It is less generally known that extravascular tissue pressure also can affect vascular volume. Patients with tense edema and hence elevated tissue pressure often are resistant to postural hypotension produced by the ganglionic blocking agents; whereas mercurial diuretics and salt-restricted diets (which deplete extracellular fluid volume) may result in disabling postural hypotension requiring a sharp reduction in dosage of the blocking agent.[5] For this reason, unless the patient is edematous it is advisable to permit moderate amounts of salt in the diet when prescribing the ganglionic blocking drugs. Accumulation of extracellular fluid in the dependent parts of the body occurring nor-

[5] Freis, E. D. Hypertension. Method of treatment. In: Current Therapy, p. 127. Edited by Conn, H. F., Philadelphia, 1955. W. B. Saunders Co.

mally during the ambulatory hours of the day may well explain the diurnal fluctuation in sensitivity so often seen in patients who are treated with blocking agents. The dose needed to control the blood pressure in the afternoon and evening often is double and sometimes quadruple the morning requirement.

The role of the sympathetic nervous system and its effects on vascular volume also may have significance in regard to congestive heart failure associated with a low cardiac output. Since in this condition the arterial pressure is normal or elevated despite the reduced cardiac output, it is apparent that the total peripheral resistance is increased. Central venous pressure is elevated, usually out of proportion to the increase in total blood volume, and there is tachycardia. It seems possible that some of these manifestations may be due to stimulation of the sympathetics through the "buffer nerve" mechanisms which are activated by a reduction in cardiac output.

A group of patients with congestive heart failure due to various causes were tested with hexamethonium.[6] The drug was given intravenously in dosages individually titrated so as to produce a significant reduction in arterial pressure. In the patients with hypertensive and arteriosclerotic heart disease, and also in patients with aortic insufficiency, there was immediate improvement in dyspnea and orthopnea as well as a decrease in venous pressure often associated with a fall in heart rate and shortening of the circulation time. As one might suspect, these beneficial results were not observed in cardiac patients with cor pulmonale or mitral stenosis. These changes, as they pertain to hypertensive heart failure, have been confirmed since by other investigators.[7,8] It was also shown that, in contrast to the hypertensive patient with compensated heart, patients with cardiac failure reacted to hexamethonium with an increase in cardiac output and a significant decrease in total peripheral resistance.[3]

This beneficial effect in congestive heart failure probably is produced by more than one mechanism. Reduction of arterial pressure reduces the cardiac work requirement. Decrease in central venous pressure and hence in right heart filling pressure "unloads" the overdistended right ventricle. In addition, Sarnoff and his coworkers recently have indicated that the heart can perform a given amount of work with less expenditure of energy at low than at high arterial pressures.[9]

This brief review has touched thus far mostly upon personal experiences. There have been many other contributors to the concepts expressed here. Sarnoff, Berglund and Sarnoff demonstrated similar relationships and also have shown by direct measurements that systemic vasoconstriction produces a shift of blood volume to the pulmonary vascular tree, whereas systemic vasodilatation induces a shift in the opposite direction.[10] They emphasized the importance of ganglionic blocking agents in the treatment of pulmonary edema. Several investigators have demonstrated that isolated venous segments in the intact forearm constrict after reflex sympathetic stimulation.[11,12] Wood, Litter and Wilkins, and also Burch, have found that venous distensibility is decreased in congestive heart failure.[13,14] Wood also has demonstrated venoconstriction in the forearm in response to pooling of blood in the legs.[15] Alexander has shown that venomotor tone is increased after hemorrhage.[16]

[6] Kelly, R. T., Freis, E. D. and Higgins, T. F. The effects of hexamethonium on certain manifestations of congestive heart failure. *Circulation*, 7: 169, 1953.

[7] Burch, R. R. The effects of intravenous hexamethonium on venous pressure of normotensive and hypertensive patients with and without congestive heart failure. *Circulation*, 11: 271, 1955.

[8] Ellestad, M. H. and Olson, W. H. Use of intravenously given ganglionic blocking agents for acute pulmonary edema. *J. A. M. A.*, 161: 49, 1956.

[9] Case, R. B., Sarnoff, S. J., Braunwald, E., Stainsby, W. N. and Taylor, Z. Hemodynamic determinants of coronary flow and myocardial oxygen consumption. *Federation Proc.*, 16: 32, 1956.

[10] Sarnoff, S. J., Berglund, E. and Sarnoff, L. C. Neurohemodynamics of pulmonary edema. III. Estimated changes in pulmonary blood volume accompanying systemic vasoconstriction and vasodilatation. *J. Appl. Physiol.*, 5: 367, 1953.

[11] Duggan, J. L., Love, V. L. and Lyons, R. H. A study of reflex venomotor reactions in man. *Circulation*, 7: 869, 1953.

[12] Page, E. B., Hickam, J. B., Sieker, H. O., McIntosh, H. D. and Pryor, W. W. Reflex venomotor activity in normal persons and in patients with postural hypotension. *Circulation*, 11: 262, 1953.

[13] Wood, J. E., Litter, J. and Wilkins, R. W. Peripheral venoconstriction in human congestive heart failure. *Circulation*, 13: 524, 1956.

[14] Burch, G. E. A method for measuring venous tone in digital veins of intact man. Evidence for increased digital venous tone in congestive heart failure. *Arch. Int. Med.*, 94: 724, 1954.

[15] Wood, J. E. and Eckstein, J. W. Peripheral venous and arteriolar responses to moderate reductions in effectively circulating blood volume in man. (Abstract.) Am. Soc. Clin. Invest., 1956.

[16] Alexander, R. S. Venomotor tone in hemorrhage and shock. *Circulation Research*, 3: 181, 1905.

The accumulated body of evidence indicates that sympathetic nervous impulses produce constriction not only of the arterioles but probably of the total vasculature. The resulting decrease in vascular volume, by raising filling pressure in the right heart, restores the cardiac output. Thus blood loss from the central circulation, either externally or internally (as in quiet standing) is quickly compensated. This mechanism, which is beneficial in the normal individual, may be detrimental in certain pathologic states—particularly in low output heart failure.

EDWARD D. FREIS, M.D. *and*
JOHN C. ROSE, M.D.,
Departments of Medicine,
Georgetown University and
Veterans Administration Hospitals,
Washington, D. C.

Clinical Studies

Kidney Function in Unilateral Pyelonephritis*

I. Clinical Data

ALEXANDER J. MICHIE, M.D. *and* CATHARINE R. MICHIE, M.D.
Philadelphia, Pennsylvania

MICROSCOPICALLY, pyelonephritis is a localized disease which may involve a part or parts of one or both kidneys. Although areas of inflammatory tissue replace the normal parenchyma, many nephrons escape complete destruction. The functional capacity of the apparently undamaged tubular remnants and of the solitary glomeruli is unknown. If any glomeruli attached to non-functioning tubules[1] contribute filtrate to the urine, the filtration rate per unit tubular function (GFR/Tm_{PAH}) will be increased.[2]† Furthermore, while partially damaged tubules may secrete p-aminohippurate (PAH) normally at low plasma concentrations (1 mg. per cent, the level used to measure effective renal plasma flow), PAH secretion may be relatively ineffectual at high plasma concentrations (60 mg. per cent, the level used to measure Tm_{PAH}). Such nephrons would cause Tm_{PAH} to diminish without changing effective renal plasma flow (ERPF). Hence, such functional deficiencies caused by disparities in nephron structure will be revealed by a significant deviation from the normal value of the ratios GFR/Tm_{PAH} and $ERPF/Tm_{PAH}$.

In unilateral pyelonephritis we postulate that the normal nephrons in the diseased kidney and the nephrons in the non-diseased mate function in an identical manner. Thus any measured difference in total function between the two kidneys will be due to (a) the number of nephrons destroyed by the infection and (b) the altered function of damaged nephrons in the diseased kidney.

In addition to the comparison of diseased and non-diseased kidneys in the same patient, the data from the chronic pyelonephritic kidneys are grouped to show the effects of time, and of various types of urinary obstructions.

Lastly, our data on the non-diseased kidney with a diseased or absent mate are tabulated to reveal the variations in the functional capacity of this kidney. The non-diseased kidney is not in a strict sense a normal kidney since its function is usually greater than one-half the mean value for two normal kidneys.[2]‡ Little is known about the stimulus which causes the hypertrophy but its effect on the solitary kidney is well established.

METHODS

Terminology. The diagnosis, non-diseased kidney, was made when the kidney never caused the patient any discomfort and produced a bacteriologically sterile urine of which the centrifuged sediment showed no increase in formed elements except red cells.§ X-ray studies showed that, while the parenchymal shadow was usually larger than normal, there was no obstruction or anatomic defect of the urinary drainage pathways in the non-diseased kidney.

A diagnosis of quiescent chronic pyelonephritis was made when two or more ureteral urine samples from the same kidney contained the same bacterial species and many leukocytes, when calyceal distortion was seen in the urograms, when the patient had not had

† Smith,[2] page 606.

‡ Smith,[2] page 545.

§ The process of ureteral catheterization always produced macro- or microscopic hematuria.

* From the Department of Physiology, New York University College of Medicine, the Harrison Department of Research Surgery of the Schools of Medicine of the University of Pennsylvania, the Urology Service of the Hospital of the University of Pennsylvania and the Surgical Service of the Children's Hospital of Philadelphia. This study was financed by grants from the Dazian Foundation and the Commonwealth Fund, and was supported further by the Harrison Department of Research Surgery of the Schools of Medicine of the University of Pennsylvania. The major portion of this work was done while the senior author was a National Research Council Fellow in the Medical Sciences in the Department of Physiology, New York University College of Medicine.

a fever for at least one week, and had had symptoms of the disease for about a month. The most common symptoms were backache, chills, fever, nausea and vomiting.

Clinical Material. All available patients with unilateral pyelonephritis were studied. For the following reasons the results from two groups of patients are omitted from this report: (1) patients with an acute exacerbation of their pyelonephritis, because marked daily variation of the clearance values made interpretation difficult, and (2) patients with hydronephrotic kidneys,* in which the stagnant urine in the large renal dead space prevented the establishment within thirty minutes of an equilibrium between plasma and ureteral urine of the test substances.[4] Such an equilibrium occurred in one patient, T. M., three hours after starting the intravenous infusion of the test substances, thus the data on this patient are included in this report. If a foreign object, such as a stone, almost filled the urinary dead space, there was no delay in the establishment of clearance equilibrium, hence data from such kidneys are also included.

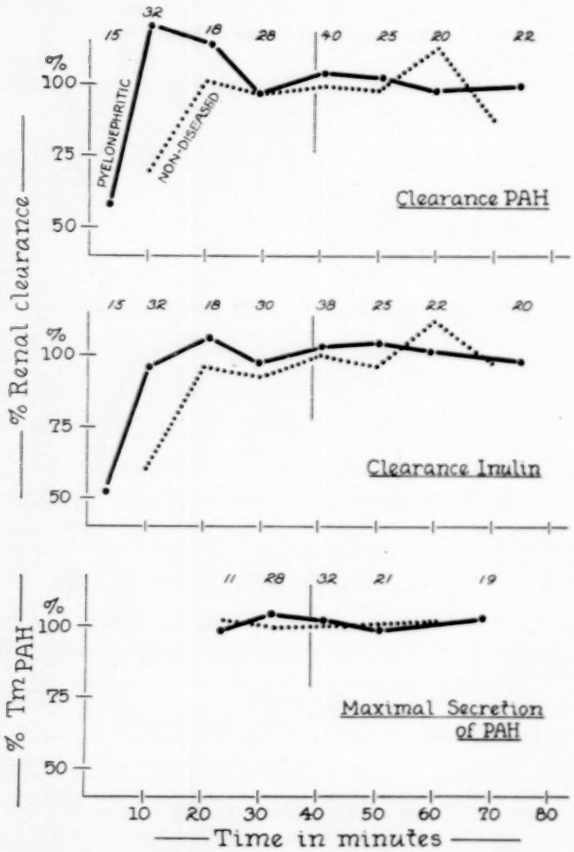

% Renal clearance
% 100 75 50
15 32 18 28 40 25 20 22
PYELONEPHRITIC
NON-DISEASED
Clearance PAH
15 32 18 30 38 25 22 20
Clearance Inulin
% Tm PAH
11 28 32 21 19
Maximal Secretion of PAH
10 20 30 40 50 60 70 80
Time in minutes

FIG. 1. The data on the non-diseased and pyelonephritic kidneys are plotted separately. The inulin and PAH clearances rise and become stable in twenty-five to thirty minutes. Tm_{PAH} varies insignificantly in the twenty-five to seventy minute period.

* The progressively rising maximal tubular excretion of diodrast in Raaschou's studies[3] may be explained by his use of the single injection method or by the presence of hydronephrosis. Equilibrium between plasma and ureteral urine of the test substances rarely occurs under these conditions. We have found, however, that only in hydronephrosis do the clearance values continue to increase thirty minutes after starting the intravenous infusion of the test substance.

Preparation. To secure an adequate flow of urine, fasting subjects drank a liter of water eight to ten hours and again one hour before the test.

Female subjects were given 10 mg. of morphine thirty minutes before cystoscopy. In males 50 mg. of procaine were injected intrathecally in such a manner as to achieve only perineal and penile anesthesia. When the effect of the morphine or spinal anesthesia was apparent, cystoscopy was performed and a No. 8 French, multieyed, whistle-tipped ureteral catheter[5] was inserted into each ureter. After removal of the cystoscope a latex urethral catheter was passed to the bladder. The routine bladder clearance was done if the patient had a solitary kidney.

Urine Collection. The bladder was rinsed with 30 ml. of saline and then 30 ml. of air. When the last drop of bladder wash fluid was expelled, the time was noted and the end of each catheter transferred simultaneously to new, labeled, graduated cylinders. During clearance measurements analysis of the bladder wash determined the amount of urine leaking around the ureteral catheters. Such a "bladder clearance" was less than 10 and usually less than 5 per cent of the clearance value of the more efficient kidney.

Blood Samples. Originally, blood samples were taken from a needle in the antecubital vein. Subsequently, the indwelling needle was inserted in the femoral artery[6] where the concentration of the test substances is equal to that in the renal artery.

Clearance Technic. The usual procedure was followed in most cases. Before starting the infusion of the test substances a blood and a urine sample were collected to determine the rate of excretion of endogenous material reacting to the inulin, mannitol or thiosulfate methods. A priming injection was followed by a constant infusion of the test substances. Thirty minutes after starting the constant infusion, a blood sample, then three ten-minute urine collections, and finally another blood sample were taken. This procedure was repeated during the measurement of the maximal tubular excretion of p-aminohippurate.

Equilibrium Clearance Technic. In seventeen patients at the termination of the initial urine collection, the priming injection was finished and the constant infusion started. In the succeeding forty-minute period frequent urine collections were obtained. These collections were terminated when the total volume of urine from the less efficient kidney reached 2 ml. During this same forty-minute interval five blood samples were obtained at eight-minute intervals. At the

termination of this forty-minute period the usual clearance technic was followed. The average clearance value obtained during the standard procedure was equated to 100. Then each clearance value was expressed as a percentage of this average value. The values between zero and five minutes, between five and fifteen minutes, fifteen and twenty-five minutes, etc. were averaged and plotted. (Fig. 1.) The numbers above the points apply only to the pyelonephritic kidneys and indicate the number of clearance periods averaged.

Chemical Methods. Glomerular filtration was originally measured with mannitol.[7] All mannitol determinations by the periodate method have been corrected by subtracting 0.28 mg. of mannitol for each milligram of p-aminohippurate in the sample.[8] Mannitol determinations by the chromotropic method[9] have been corrected for the 10 per cent reabsorbed by the tubules.[10] For a short time thiosulfate[11] was used to measure the filtration rate. Since p-aminohippurate interferes with the analysis of thiosulfate,[12] a series of correction factors were used to compensate for the interference of varying concentrations of PAH in the thiosulfate analysis. Subsequently, inulin[13,14] was used to measure the filtration rate.

PAH[15] was used to measure effective renal plasma flow and maximal tubular excretion.

RESULTS

Previously we showed that the non-diseased kidney requires twenty-five minutes to effect a constant clearance of PAH and inulin after beginning a constant intravenous infusion of these substances.[4] This study of single kidneys was continued and now includes ten pyelonephritic and fifteen non-diseased kidneys, in which Tm_{PAH} varies from 20 to 186 per cent of half the mean value for two normal kidneys.[2]* The clearance values for the pyelonephritic kidneys rise toward equilibrium more rapidly (Fig. 1) but they overshoot the equilibrium value and attain a steady state five minutes after the non-diseased kidneys. Although the data for Tm_{PAH} between zero and thirty minutes are not available, this value is constant† throughout the thirty- to seventy-minute interval. Thus in the measurement of GFR, ERPF and Tm_{PAH} with a suitable constant infusion of the test substances, an equilibrium between plasma and ureteral urine is established within thirty minutes by both the pyelonephritic and the non-diseased kidney.

Chronic pyelonephritis of less than six months' duration (Table I) causes a slight decrease of all measured renal functions. This is evident when the opposite kidney is not affected by disease. Statistical analysis[16] of the functional difference between the two kidneys reveals a significant diminution of GFR and a suggestive drop in ERPF and Tm_{PAH} in the diseased kidney. But,

TABLE I
UNILATERAL CHRONIC PYELONEPHRITIS OF SHORT DURATION

	Glomerular Filtration Rate (ml./min./1.73 M.²)		Effective Renal Plasma Flow (ml./min./1.73 M.²)		Maximal Tubular Secretion of p-Aminohippurate (mg./min./1.73 M.²)	
Patient	Non-diseased	Diseased	Non-diseased	Diseased	Non-diseased	Diseased
M. M.	68.7	56.3	216	187	30.3	21.6
K. C.	64.0	55.8	310	286	49.2	48.9
E. M.	57.3	51.6	286	269	42.4	39.9
M. H.	43.5	41.0	227	234	51.1	23.4
S. H.	65.9	59.5	362	339	45.7	40.9
Difference						
Mean	7.0 ± 3.6		17.2 ± 14.2		8.8 ± 11.0	
Significance	$P < 0.02$		$P < 0.06$		$P < 0.16$	
Total Renal Function						
Patients	112.7 ± 17.3		543 ± 118		78.7 ± 17.1	
Normal subjects	116.5 ± 28.1		640 ± 164		78.9 ± 13.2	
Comparison of means	$P < 0.8$		$P < 0.3$		$P < 1.0$	

Note: Uncomplicated unilateral pyelonephritis of less than six months' duration. The function of the pyelonephritic kidney is always less than the non-diseased kidney; but there is no difference in the patients' total renal function and that of the normal subjects.

when the total renal function of these five patients with unilateral pyelonephritis is compared with the normal,[2]* there is no significant decrement in renal function. Therefore a compensatory increase in function of the non-diseased kidney equalizes the decrement in the diseased kidney, the net result being no change in total renal function.

When the pyelonephritic process has persisted for more than six months (Table II) the ravages of this disease are obvious. In these patients the total renal function (GFR, ERPF and Tm_{PAH}) is significantly less than the normal values. Thus compensatory increase in function in the non-diseased kidney fails to balance the loss in function on the diseased side. Usually the longer the duration of the disease the greater the decrement in renal function.

The extent of renal dysfunction in calculous pyelonephritis is determined by the position of

* Smith,[2] page 545.

† See footnote, page 180.

* Smith,[2] page 545, mixed sexes.

the stone. (Table III.) Staghorn and calyceal stones frequently cause a minimal diminution* in renal function. But severe impairment of renal function occurs when pyelonephritis is associated with obstructing renal pelvic and ureteral stones. This fact is emphasized by the fourfold increase in Tm_{PAH} in patient J. M. following ureterolithotomy, whereas complete division of the kidney for removal of a staghorn calculus in subject J. B. was unassociated with any change in Tm_{PAH}.

A striking reduction in kidney function (Table IV) was present in our two cases of nephrocalcinosis associated with pyelonephritis and erosion of the renal papillae. In neither patient was there any obstruction to urine flow from the kidney. While the daily ingestion of 3 gm. of sulfathiazole in one of the patients, M. S., did not eradicate the infection, there was a diminution in the pyuria. This was associated in each kidney with an approximate 46 per cent increase in Tm_{PAH} yet ERPF continued to decline. There is no significant alteration in renal function in mild nephrocalcinosis uncomplicated by pyelonephritis or by erosion of the renal papillae. (Tables IV and V.)

With one exception, patient M. M., Tm_{PAH} in the non-diseased kidneys (Table VI) was greater than 39.5 mg./minute, one-half the mean for two normal kidneys. In J. E., six months after nephrectomy, the remaining kidney functioned almost as well as two normal kidneys. In no case

TABLE II

CHRONIC PYELONEPHRITIS OF LONG DURATION

Patient	Glomerular Filtration Rate (ml./min./1.73 M.²) Right	Glomerular Filtration Rate (ml./min./1.73 M.²) Left	Effective Renal Plasma Flow (ml./min./1.73 M.²) Right	Effective Renal Plasma Flow (ml./min./1.73 M.²) Left	Maximal Tubular Secretion of p-Aminohippurate (mg./min./1.73 M.²) Right	Maximal Tubular Secretion of p-Aminohippurate (mg./min./1.73 M.²) Left
S. S.	18.5	29.6	68	109	11.6	19.1
D. F.	....	77.0	...	260	.....	46.7
	....	60.6	...	246	.....	51.9
	....	55.5	...	229	.....	45.5
T. M.	6.0	22.5	19	97	−2.5	8.4
	1.5	15.2	8	94	0.4	9.1
M. R.	13.6	46.3*	58	216*	14.9	56.9*
	14.2	45.9*	62	202*	14.5	47.2*
E. B.	45.1	45.0	222	221	42.8	37.8
	57.8	63.7	280	296	34.1	35.7
Pyelonephritic kidney						
Long duration	39.9 ± 21.7		174 ± 107		26.8 ± 13.6	
Short duration	52.8 ± 7.4		263 ± 57		34.9 ± 11.9	
Comparison of means	$P < 0.3$		$P < 0.2$		$P < 0.4$	
Total renal function						
Patients	71.4 ± 34.1		312 ± 180		51.9 ± 17.4	
Normal subjects	116.5 ± 28.1		640 ± 164		78.9 ± 13.2	
Comparison of means	$P < 0.01$		$P < 0.001$		$P < 0.001$	

Note: Uncomplicated pyelonephritis of more than six months' duration. The decrement in renal function is greater when the disease has been present for more than six months. In patients with a single kidney the clearance values should be compared with the mean for two normal kidneys, as in patients, D. F., J. B., M. H.′, R. K., J. N., E. G., J. E. and M. G. (Tables III, IV and VI.)

* Non-diseased kidney.

TABLE III

CHRONIC PYELONEPHRITIS WITH STONES

Patient	Glomerular Filtration Rate (ml./min./1.73 M.²) Right	Glomerular Filtration Rate (ml./min./1.73 M.²) Left	Effective Renal Plasma Flow (ml./min./1.73 M.²) Right	Effective Renal Plasma Flow (ml./min./1.73 M.²) Left	Maximal Tubular Secretion of p-Aminohippurate (mg./min./1.73 M.²) Right	Maximal Tubular Secretion of p-Aminohippurate (mg./min./1.73 M.²) Left
	Staghorn and Calyceal					
J. B.	.....	150.0	....	1040	.....	67.7
	.....	94.2	....	444	.....	66.5
E. C.	48.0	70.5*	325	352*	40.7	59.2*
N. T.	36.8	45.8*	195	236*	33.2	46.2*
E. M.′	50.8*	52.0	299*	297	55.0*	52.0
D. W.	23.5	71.2*	121	233*	22.7	42.6*
B. S.	2.9	17.5	8	11	−0.4	1.8
	Pelvic and Ureteral					
J. M.	5.0	53.8	27	258	4.0	39.0
	23.4	45.0	106	165	15.2	32.4
P. V.	25.3	4.7	97	15	7.5	−4.6
K. K.	7.6	50.6*	52	256*	10.4	54.5*
H. S.	0.5	52.0*	1	211*	0.1	38.5*
M. H.′	.....	19.4	....	119	.....	13.6
	.....	21.3	....	122	.....	18.5
R. K.	.....	43.1	....	249	.....	22.3

Note: Chronic pyelonephritis complicated by stones. With the exception of patient D. W., staghorn and calyceal stones cause a minimal decrement in renal function. Pelvic and ureteral stones partially obstruct the total outflow of urine and rapidly depreciate renal function.

* Non-diseased kidney.

* We cannot explain the reduced function in patient D. W. However, in B. S., who had a bladder stone removed fifteen years prior to this study, the marked diminution in function may be secondary to ureterovesical obstruction. Although the hydroureters and hydronephrosis subsided following removal of the bladder stone, restoration of renal function may not have occurred.

did the function of one kidney exceed that of two normal kidneys. Generally, the poorer the efficiency of the diseased kidney, the greater the function of the non-diseased mate.

COMMENTS

Physiologic Aspects. In pyelonephritis clusters of inflammatory cells may partially or completely isolate groups of normal appearing nephrons. Urine flow from these nephrons may be retarded by passing through this inflammatory tissue. If so, then such urine would arrive in the renal pelvis sometime after that formed by nephrons with non-obstructing collecting tubules. Accordingly, more time would elapse between the beginning of the test infusion and the achievement of a constant concentration of the test substance in the pelvic urine, that is, the clearance equilibrium time would be prolonged. But the clearance equilibrium time is almost identical for the pyelonephritic and the non-diseased kidney. (Fig. 1.) Thus nephrons surrounded by inflammatory tissue either form an insignificant amount of urine or excrete urine as rapidly as the uninvolved nephrons.

In other areas linear infiltrates of inflammatory cells obliterate peritubular capillaries, and separate, compress and damage tubules without apparently affecting the neighboring glomeruli. Theoretically, such glomeruli would add to the pelvic urine unaltered or partially processed filtrate which would increase the GFR/Tm_{PAH} ratio. But statistically, the GFR/Tm_{PAH} ratio of the pyelonephritic kidney (1.36 ± 0.45, $n = 18$) is practically the same ($P < 0.8$) as that of the non-diseased kidney (1.32 ± 0.43, $n = 13$). (Table VII.) Again, theoretically, the damaged or compressed tubules may not effectively excrete PAH at high blood concentrations. The urine they produce would increase the ERPF/Tm_{PAH} ratio. However there is no statistical difference* ($P < 0.4$) in the ERPF/Tm_{PAH} ratio between the pyelonephritic (6.82 ± 1.88, $n = 18$) and the non-diseased kidney (6.35 ± 1.69, $n = 13$). (Table VII.) This indicates, as others have shown,[3,17,18] that glomerular and tubular function as well as effective renal plasma flow maintain the same proportions in the pyelonephritic and non-diseased kidney.

* Nor is there any significant difference ($P < 0.4$) in the GFR/ERPF ratio of the pyelonephritic (20.0 ± 3.4, $n = 18$) and the non-diseased kidney (21.0 ± 5.0, $n = 13$).

This identity of the functional characteristics of the diseased and non-diseased kidney indicates that the working units in each kidney are similar. Thus the pyelonephritic kidney, when Tm_{PAH} is greater than 10 mg./minute, is less efficient only because it contains fewer functioning nephrons. If these conclusions are valid, then at the same moment the concentration of the test substances would be identical in the pelvic urine of each kidney in a patient with unilateral pyelonephritis. This criterion was satisfied* in seven of the eleven patients with a pyelonephritic and a hypertrophic non-diseased kidney.[19] Accordingly, in these seven patients the degree of nephron hyperactivity must be equivalent in both the diseased and non-diseased kidney.[20]

TABLE IV
MEDULLARY NEPHROCALCINOSIS

Patient	Glomerular Filtration Rate (ml./min./1.73 M.²)		Effective Renal Plasma Flow (ml./min./1.73 M.²)		Maximal Tubular Secretion of p-Aminohippurate (mg./min./1.73 M.²)	
	Right	Left	Right	Left	Right	Left
	Pyelonephritis					
M. S.	15.8	62.1	126	281	9.9	27.0
	20.2	47.7	110	246	11.4	29.2
	16.5	42.9	85	208	14.7	38.7
J. N.	....	20.8	...	128	....	3.1
	No Pyelonephritis					
M. R.′:						
Upper	8.8	8.3	53	52	5.7	4.8
Lower	21.1	66.0	139	414	26.3	36.4
J. L.	*115**		*753*		*63.6*	
	137		*565*		*49.0*	
B. E.	*101*		*429*		*71.0*	

Note: When nephrocalcinosis is complicated by pyelonephritis with pyramidal erosion, renal function is severely impaired. In the absence of pyelonephritis, little or no diminution in renal function occurs unless there are more than 50 calcific particles in each pyramid (second examination of patient J. L.).

* Figures in italics indicate determinations for both right and left kidneys.

* By "identical" we mean that the concentration of the test substances in the pelves of the two kidneys was within ±5 per cent of their mean value.

TABLE V

MEDULLARY NEPHROCALCINOSIS WITHOUT PYELONEPHRITIS
(FUNCTION COMPARED WITH NORMAL)

Patient	Date	Glomerular Filtration Rate (ml./min.)	Effective Renal Plasma Flow (ml./min.)	Maximal Tubular Excretion of p-Aminohippurate (mg./min.)
M. R.′	1/14/47	104.	658	73.2
J. L.*	11/28/49	115.	753	63.6
B. E.	3/11/52	101.	429	71.0
Mean		107 ± 1.0	613 ± 168	69.3 ± 4.7
Normal mean		116.5 ± 28.1 (n = 50)	640 ± 164 (n = 40)	78.9 ± 13.2 (n = 40)
Comparison with normal:				
t		0.606	0.267	1.226
P less than		0.6	0.8	0.3

Note: Each datum is the average of three consecutive urine collection periods and is corrected to a surface area of 1.73 M.² Each patient appears once.

* In this patient data from the first study were used. At that time there were 2 or 3 calcific deposits in each renal pyramid. At the last examination, two years later, there were 50 to 100 calcific deposits in each pyramid.

TABLE VI

NON-DISEASED KIDNEYS

Patient	Glomerular Filtration Rate (ml./min./1.73 M.²)	Effective Renal Plasma Flow (ml./min./1.73 M.²)	Maximal Tubular Secretion of p-Aminohippurate (mg./min./1.73 M.²)
M. M.	68.7	216	30.3
K. C.	64.0	310	49.2
K. K.	50.6	256	54.5
E. M.	57.3	286	42.4
M. H.	43.5	227	51.1
E. G.	69.6	317	40.7
S. H.	65.9	362	45.7
N. T.	45.8	236	46.2
E. M.	50.8	259	55.0
J. E.	95.6	564	73.5
	73.9	496	69.8
D. W.	71.2	233	42.6
M. G.	84.0	498	49.1
M. R.	46.3	216	56.9
	45.9	202	47.2
Mean Non-diseased kidney	60.9 ± 12.6	303 ± 98	48.0 ± 9.1
$\frac{2 \text{ Normal kidneys}}{2}$	58.3 ± 14.1	320 ± 82	39.5 ± 6.6

Note: Hypertrophic non-diseased kidneys. In calculating the mean each kidney appears once. When a kidney was restudied the second examination is used in the summation for the mean. The standard deviations for $\frac{2 \text{ normal kidneys}}{2}$ are obtained from the data on normal subjects (each subject theoretically has two normal kidneys) by assuming that the coefficient of correlation is the same.

Clinical Aspects. Incomplete obstruction to urine flow from an entire kidney accelerates the renal damage caused by pyelonephritis.[21] The obstructed kidneys of the patients with pelvic and ureteral stones (Table III) reveal marked deterioration of the measured renal functions. Conversely, partial blockage from a segment of the kidney by a staghorn or calyceal stone causes only a slight decrease in renal efficiency. (Table III and M. R.′, J. L. and B. E., Table IV). Roentgen evidence suggests that pyramidal, calyceal and, frequently, staghorn stones cause no apparent obstruction to urine flow. In the patients studied when pyelonephritis is combined with partial obstruction to urine flow from a segment of the kidney, for example, calyceal stone, there is a slow regression in renal efficiency. But when pyelonephritis is associated with ureteral obstruction, there is a rapid degradation in renal function.

Erosion of the renal pyramids effectively reduces the functional capacity of the kidney (M. S. and J. N., Table IV). With pyramidal erosion there is probably destruction of all nephrons with loops descending into the ulcerated pyramids.[22] When this destruction is coupled with constricted and obstructed collecting tubules, marked deterioration of renal function must occur.

CONCLUSIONS

In the chronic pyelonephritic and the non-diseased kidney equilibrium between plasma and ureteral urine of inulin and p-aminohippurate occurs within thirty minutes. The equilibration time is independent of over-all renal function and indicates that there is no delayed

TABLE VII

CLEARANCE RATIOS

MUTUAL COMPARISONS OF NON-DISEASED, PYELONEPHRITIC AND NORMAL KIDNEYS

Patient	Date	GFR/ERPF	GFR/Tm_{PAH}	ERPF/Tm_{PAH}
		Non-Diseased Kidneys		
M. M.	7/23/45	31.8	2.27	7.13
K. C.	10/24/45	20.6	1.30	6.30
E. M.	5/20/46	20.0	1.35	6.75
K. K.	6/17/46	19.8	0.928	4.70
E. G.	9/16/46	22.0	1.71	7.79
M. H.	7/ 2/46	19.2	0.851	4.44
N. T.	1/13/47	19.4	0.991	5.11
E. M.	3/31/47	17.0	0.924	5.44
S. H.	9/30/46	18.2	1.44	7.92
D. W.	11/ 6/47	30.6	1.67	5.47
M. R.	3/ 1/49	22.7	0.972	4.28
J. E.	11/ 2/47	14.9	1.06	7.11
M. G.	11/11/47	16.9	1.71	10.14
Mean		21.0 ± 5.0	1.32 ± 0.43	6.35 ± 1.69 (n = 13)
		Normal Kidneys		
Mean		18.2 ± 4 (n = 40)	1.54 ± 0.4 (n = 49)	8.28 ± 2.2 (n = 41)
Comparison with normal kidneys:				
t		2.014	1.705	2.851
P less than		0.05	0.1	0.01
		Pyelonephritic Kidneys		
M. M.	7/23/45	30.1	2.61	8.66
K. C.	10/24/45	19.5	1.14	5.85
E. M.	5/20/46	19.2	1.29	6.74
M. H.	7/ 2/46	17.5	1.75	10.00
S. H.	9/30/46	17.6	1.45	8.29
E. B. (r)	9/12/49	20.6	1.70	8.21
E. B. (l)	9/12/49	21.5	1.78	8.29
D. F.	4/ 8/46	24.2	1.22	5.03
M. H.'	12/22/47	17.5	1.15	6.59
R. K.	11/25/47	17.3	1.93	11.17
M. R.	3/ 1/49	22.9	0.979	4.27
J. B.	11/21/45	21.2	1.42	6.68
N. T.	1/13/47	18.9	1.11	5.87
E. M.'	3/31/47	17.5	1.00	5.71
D. W.	11/ 6/47	19.4	1.04	5.33
K. K.	6/17/46	14.6	0.731	5.00
M. S. (r)	1/ 5/47	19.4	1.12	5.78
M. S. (l)	1/ 5/47	20.6	1.11	5.37
Mean		20.0 ± 3.4	1.36 ± 0.45	6.82 ± 1.88 (n = 18)
Comparison with normal kidneys:				
t		1.622	1.552	2.405
P less than		0.2	0.2	0.02
Comparison with non-diseased kidneys:				
t		0.980	0.370	1.063
P less than		0.4	0.8	0.4

Note: Each datum is the average of three consecutive urine collection periods and is corrected to a surface area of 1.73 $M.^2$ Each patient appears once. In repeat studies only the data from the last experiment are used.

excretion from a large number of nephrons in the diseased kidney.

Statistical comparison of the filtration rate per unit of tubular excretory tissue (GFR/Tm_{PAH}), the filtration fraction (GFR/ERPF) and the effective renal plasma flow per unit of tubular excretory tissue ($ERPF/Tm_{PAH}$) shows no significant difference between the diseased kidney and its non-diseased mate, and indicates that in chronic pyelonephritis complete loss of nephron function predominates over specific impairment of glomerular or tubular function.

Hypertrophy of non-diseased nephrons in both kidneys tends to compensate for the slight decrease in kidney function associated with pyelonephritis of short duration. When this disease has been present for more than six months, hypertrophy fails to balance the functional deficit.

When a stone partially obstructs the ureteropelvic junction or the ureter of a pyelonephritic kidney, it accelerates the regression of renal function. However if the stone is anchored in a calyx the regression in renal function is less rapid, and may indeed occur very slowly.

Erosion of the renal pyramids was associated with an extensive reduction in renal function in the two cases studied.

In unilateral renal disease the increase in function of the non-diseased kidney suggests that the degree of hypertrophy of the various undamaged nephrons is not uniform. Generally, the greater the diminution in function of the diseased kidney, the greater the degree of hypertrophy in the non-diseased mate. Neither the function of a solitary non-diseased kidney nor the combined function of the non-diseased plus the pyelonephritic kidney in the same patient has ever been observed to exceed the function of two normal kidneys.

CASE REPORTS

M. M., a thirty-five year old woman with a surface area of 1.41 M.^{2}, had a ptotic right kidney. In this patient back pain developed at the right costovertebral angle, associated with fever, pyuria and bacilluria eight weeks before the clearance examination. Within two weeks of the onset, a sulfonamide drug had controlled the infection and pain. The clearance was done on July 23, 1945.

K. C., a twenty-eight year old woman with a surface area of 1.84 M.^{2} and a blood pressure of 125/80, showed roentgenographic evidence of slight anatomic obstruction of the right urinary tract. She complained of pain in the right flank, urinary urgency and frequency of ten weeks' duration. While this patient had been asymptomatic for two weeks prior to the kidney test, Escherichia coli was cultured from the right kidney urine despite protracted and continuous sulfonamide therapy. The clearance was performed on October 24, 1945.

E. M., a fifty-two year old man with a surface area of 1.94 M.^{2} and a blood pressure of 132/80, had a small left ureteral stone associated with renal colic for thirty days prior to the insertion of a left ureteral catheter. One day later chills, fever and a constant ache in the left flank developed which disappeared three days after the catheter was removed. The stone passed shortly after the catheter was withdrawn. At that time the patient was given penicillin and a sulfonamide. The renal clearance was performed May 20, 1946, eight days after the symptoms had disappeared.

M. H., in this sixteen year old girl with a surface area of 1.49 M.^{2} and a blood pressure of 120/80, urinary frequency, chills, fever and pain in the left flank developed five months postpartum. The symptoms disappeared two days after sulfonamide therapy was begun. X-rays revealed a slight obstruction at the ureteropelvic junction without hydronephrosis. The clearance was done on July 2, 1946, one month after the symptoms had disappeared.

S. H., a twenty-nine year old man with a surface area of 1.73 M.^{2} and a blood pressure of 112/74, suddenly experienced a colicky pain in the right flank forty days prior to the kidney study. Following the insertion of a right ureteral catheter for forty-eight hours asymptomatic right bacilluria and pyuria occurred. Nine days later, on September 30, 1946, clearance measurements were made.

S. S., a thirty-three year old woman with a surface area of 1.58 M.^{2} and a blood pressure of 225/155, had a horseshoe kidney. Following a septic abortion in 1928, an intractable bilateral kidney infection developed. The patient's hypertension was recognized in 1930. Except that the ureters crossed the joining renal segment anteriorly, no anatomic obstruction to urine flow was evident. The clearance was done on October 8, 1945.

D. F., a twenty-two year old man, had a right nephrectomy in 1938 because of marked hydronephrosis. Subsequently his chronic left pyelonephritis was complicated by a renal stone which was excised. A left ureteral stricture occurred and had to be dilated periodically during the next two to three years. A bladder stone developed and was removed in 1943. Since 1943 there was no x-ray evidence of obstruction to urine flow from the left kidney. In December, 1945,

a prostatic median bar was excised. Then chemotherapy of three months' duration eradicated the urinary tract infection by April, 1946. The initial clearance was done on October 10, 1945, when the surface area was 1.90 M.^{2} and the blood pressure was 130/85; the second clearance on October 17, 1945, when the surface area was 1.90 M.^{2} and the blood pressure 145/85; and the third clearance on April 8, 1946, when the surface area was 1.98 M.^{2} and the blood pressure was 130/82.

T. M., a twenty-three year old man with a surface area of 1.73 M.^{2} and a blood pressure of 130/82, had a megalobladder, bilateral hydroureters and hydronephrosis because of a urethral valve. Following a perineal urethrostomy the bladder became small but there was no contraction of the hydroureters or hydronephrosis. Clearances were done to see if urinary excretion would be constant after a three-hour equilibration period during which the blood concentration of the test substances was kept constant. Because clearance equilibrium had been established we included the data on this patient.[4] The initial clearance was performed on February 4, 1946, and the second on April 1, 1946.

M. R., a fifty-five year old woman, first noted pyuria in 1943. Since then she had experienced bimonthly or monthly episodes of malaise and generalized weakness. A sulfonamide was administered in 1947 and her symptoms and bacilluria disappeared by December of that year. The initial clearance was done on January 27, 1948, when the surface area was 1.79 M.^{2} and the blood pressure was 132/84; the second clearance was performed on March 1, 1949, when the surface area was 1.76 M.^{2} and blood pressure was 144/82.

E. B., a twenty-nine year old woman, experienced chills, fever and urinary frequency about two weeks after delivery of her second child. Following therapy the symptoms disappeared for two months but recurred three months prior to the first kidney test. In spite of therapy the bacilluria persisted until October, 1948. X-ray studies failed to demonstrate an obstructive uropathy. The initial clearance was done on May 27, 1948, when the surface area was 1.55 M.^{2} and the blood pressure was 134/90; the second clearance was performed on September 12, 1949, when the surface area was 1.60 M.^{2} and the blood pressure was 132/84.

J. B., a fifty-two year old man, had a right nephrectomy for a staghorn calculus in 1927. He was asymptomatic until 1939 when a throbbing ache developed in the left flank associated with intermittent chills and fever. These symptoms disappeared following the removal of a staghorn calculus from the left kidney on October 15, 1945. The initial clearance was done during an asymptomatic interval on October 5, 1945, when he had a surface area of 1.72 M.^{2} and a blood pressure of 110/70; the second clearance was performed on November 21, 1945, when the surface area was 1.74 M.^{2} and the blood pressure was 130/85.

E. C., a fifty-two year old man with a surface area of 1.61 M.^{2} and a blood pressure of 160/100, had vague ache in the right flank of several years' duration. A small stone, 1 cm. in diameter, was adherent to the renal pelvic mucosa near a pyramid. It caused no obstruction to the flow of urine. At the time of the kidney tests on January 10, 1947, the urine was bacteriologically sterile.

N. T., a fifty-four year old man with a surface area of 1.86 M.^{2} and a blood pressure of 124/84, had two stones in his right kidney as seen on x-ray films taken in 1932. Each stone, measuring approximately 1 cm. in diameter, was in a calyx. Reexamination in 1947 showed that they had not changed. They had caused no symptoms. At the time of the tests on January 13, 1947, the urine was free of bacteria.

E. M.′, a forty-five year old man with a surface area of 1.64 M.^{2} and a blood pressure of 105/70, had symptoms of pain in the right upper quadrant associated with sporadic episodes of terminal hematuria for fifteen years. A large staghorn calculus filled most of the renal pelvis and infundibula in an x-ray film taken in 1945. The roentgenographic picture in 1947 was similar to that in 1945. The clearance was done on March 31, 1947.

D. W., a sixty year old man with a surface area of 1.92 M.^{2} and a blood pressure of 120/75, had a calyceal stone in all but two infundibula of the right kidney since 1943. During the four-year period prior to the renal clearance measurements, he had repeated episodes of pain in the left costovertebral angle and flank associated with chills, fever and pyuria. The tests were done on November 6, 1947.

B. S., a fifty-three year old woman with a surface area of 1.63 M.^{2} and a blood pressure of 128/68, had a bladder stone removed thirteen years prior to the clearance test. At that time the patient also had hydroureters and hydronephrosis. Subsequently, the development of bilateral staghorn calculi obliterated the increased renal dead space. Although the pyuria and bacilluria persisted, she was asymptomatic. The renal clearance was performed on May 10, 1949.

J. M., a fifty-seven year old man, had right renal colic for four weeks before he came to the hospital. X-ray films showed bilateral staghorn calculi and a large calculus lodged in the right ureteropelvic junction. The latter stone was excised one week after the first clearance test. The initial clearance was done on

September 20, 1945, when the surface area was 1.75 M.² and the blood pressure was 150/80; the second examination was done on November 16, 1945, when the surface area was 1.75 M.² and the blood pressure was 150/88.

P. V., a forty-five year old man with a surface area of 1.37 M.² and a blood pressure of 110/85, had spontaneously passed many stones during a twenty-year period. Many nephro- and ureterolithotomies had been done on each side during this same period. The patient spontaneously passed a right ureteral calculus two weeks before the clearance test which was done on October 31, 1945.

K. K., a forty-nine year old woman with a surface area of 1.70 M.² and a blood pressure of 120/72, had a right staghorn calculus whose intrapelvic protrusion obstructed the ureteropelvic junction. The clearance was performed on June 17, 1946, six weeks after removal of the intrapelvic portion of the stone.

H. S., a sixty-eight year old woman with a surface area of 1.65 M.² and a blood pressure of 190/90, had a right staghorn calculus whose intrapelvic protrusion occluded the ureteropelvic junction. X-ray films first demonstrated the stone nine years previously. At the time of the clearance on October 7, 1946, very little urine drained through the right ureteral catheter. An intravenous urogram failed to show dye excretion on the right side.

M. H.′, a sixty year old woman, had a large intrapelvic right renal stone which blocked the ureteropelvic junction. A nephrostomy was performed but little or no urine drained through the tube. No stones or obstruction to urine flow were present on the left. There were many leukocytes and bacteria in the urine obtained from the left kidney. A parathyroid adenoma was removed one week after the first renal clearance which was done on November 18, 1947, when the patient's surface area was 1.54 M.² and the blood pressure was 122/80. The second examination was done on December 22, 1947, when the surface area was 1.61 M.² and the blood pressure 126/89.

R. K., a fifty-three year old man with a surface area of 1.66 M.² and a blood pressure of 138/72, had a large cancer of the bladder which completely occluded the right and partially occluded the left ureteral orifices. The right kidney was removed eight months before an indwelling catheter was inserted in the left ureter. The clearance tests were performed on November 25, 1947, three weeks after intubation of the left ureter. During this period the hydronephrosis subsided but the pyelonephritis continued.

M. S., a forty-eight year old woman, for many years had passed spontaneously ureteral calculi associated with pain in the right or left flank. X-ray films showed that the pyramids were replaced by cavities which extended deeply into the medullary substance, which was dappled with calcific particles. Following the first clearance the patient was given 1.0 gm. of sulfathiazole every eight hours. The pyuria and bacilluria diminished but did not disappear. The patient was asymptomatic except when the medullary calcific particles passed through the ureters. She did not have diabetes. At the time of the first clearance on June 24, 1946, the surface area measured 1.80 M.² and the blood pressure was 125/85; the second clearance was done on July 24, 1946, when the surface area was 1.80 M.² and the blood pressure was 120/85; and the third was performed on January 5, 1947, when the surface area was 1.86 M.² and blood pressure was 140/80.

J. N., a twenty-one year old woman with a surface area of 1.18 M.² and a blood pressure of 105/60, apparently had uninfected spotty medullary nephrocalcinosis as seen on x-ray films taken eight years before the clearance examination which was performed on December 4, 1947, (no cultures reported). Eventually, complete erosion of the medulla occurred associated with spontaneous passage of many stones. Occasionally, adherent stones grew and filled the cavities of the eroded medullas. On the right side stones replaced most of the renal parenchyma and this kidney was excised. On two occasions stones had been excised from the left kidney. The patient was asymptomatic except when stones were passing through the ureter. The duration of the infection was unknown. Probably because of the numerous operations four or five different bacteria were found in the urine.

M. R.′, a thirty-six year old woman with a surface area of 1.64 M.² and a blood pressure of 120/80, had no symptoms of renal disease. This patient had four separate kidneys and ureters. Clearance tests were done on January 14, 1947.

J. L. had polydipsia since birth and ingested 4 to 8 gm. of sodium citrate daily to prevent the development of acidosis. Urine cultures were always bacteriologically sterile. With the passage of time the sodium citrate requirement diminished. On the initial examination, November 28, 1949, when she was three years old, there were two to three calcific particles, and at the last study, October 15, 1951, when the patient was five years old, there were 50 to 100 calcific particles in each renal pyramid. On the first examination the surface area was 0.667 M.² and the blood pressure was 100/70; on the second examination the surface area measured 0.805 M.²

B. E., a sixteen year old boy with a surface area of 1.28 M.² and a blood pressure of 120/80, was asymptomatic. Nephrocalcinosis was accidently discovered when an abdominal x-ray film was obtained for other

reasons. Renal clearances were done on March 11, 1952.

E. G., a thirty-seven year old man with a surface area of 1.86 M.² and a blood pressure of 150/94, had a right nephrectomy one month prior to the renal clearances which were done on September 16, 1946. This patient was not classified as a hypertensive because his blood pressure was elevated only during the clearance tests.

J. E., a twenty-eight year old man, had a right nephrectomy one week before the first examinations were made. At the time of the initial clearance, October 15, 1947, the surface area was 2.06 M.² and the blood pressure was 130/75. At the last study, November 2, 1947, the surface area was 2.05 M.² and the blood pressure measured 126/68.

M. G., a forty-seven year old woman with a surface area of 1.50 M.² and a blood pressure of 122/80, had her right kidney removed two weeks before the clearance studies which were performed on November 11, 1947.

Acknowledgment: The authors are grateful to Dr. Homer W. Smith for his kind advice and encouragement. They are indebted to Drs. Jean Oliver, Edward Rose, T. F. McNair Scott, Otto Rosenthal and Lewis Barness for helpful criticisms in writing this paper.

Patient material was generously made available by the late Dr. Howard Jeck and by Dr. Robert Hotchkiss of the Urology Service (Cornell) of Bellevue Hospital. Additional subjects were studied through the kindness of Drs. I. S. Ravidin, Joseph Stokes, C. E. Koop, Jeanette McConnell Shorey and Fred Harvie, all of the Schools of Medicine of the University of Pennsylvania.

The authors gratefully acknowledge the technical assistance of Drs. John G. Gislason and Hans Zinsser and also Mrs. Dryden Morse, B. A., and Miss Marie Ragni, B. A.

REFERENCES

1. Oliver, J. and Luey, A. S. Plastic studies in abnormal renal architecture. *Arch. Path.*, 19: 1, 1935.
2. Smith, H. W. The Kidney, Structure and Function in Health and Disease. New York, 1951. Oxford University Press.
3. Raaschou, F. Studies of Chronic Pyelonephritis. Copenhagen, 1948. Ejnar Munksgaard.
4. Michie, A. J. and Michie, C. R. Attainment of equilibrium between plasma and urine, with reference to measurement of renal clearances. *J. Urol.*, 66: 518, 1951.
5. Chasis, H. and Redish, J. Function of the separate kidneys in hypertensive subjects. *Arch. Int. Med.*, 70: 738, 1942.
6. Brun, C., Hilden, T. and Raaschou, F. The significance of the difference in systemic arterial and venous plasma concentrations in renal clearance methods. *J. Clin. Investigation*, 28: 144, 1949.
7. Smith, W. W., Finkelstein, N. and Smith, H. W. Renal excretion of hexitols (sorbitol, mannitol, and dulcitol) and their derivatives (sorbitan, isomannide, and sorbide) and of endogenous creatinine-like chromogen in dog and man. *J. Biol. Chem.*, 135: 231, 1940.
8. Barker, H. G. and Clark, J. K. Effect of p-aminohippurate on mannitol determinations by the periodate-iodide-thiosulfate method. *Proc. Soc. Exper. Biol. & Med.*, 64: 120, 1947.
9. Corcoran, A. C. and Page, I. H. A method for the determination of mannitol in plasma and urine. *J. Biol. Chem.*, 170: 165, 1947.
10. Berger, E. Y., Farber, S. J. and Earle, D. P., Jr. Renal excretion of mannitol. *Proc. Soc. Exper. Biol. & Med.*, 66: 62, 1947.
11. Newman, E. V., Gilman, A. and Philips, F. S. The renal clearance of thiosulfate in man. *Bull. Johns Hopkins Hosp.*, 79: 229, 1946.
12. Elliott, S. R., II, and Scott, H. W., Jr. Effect of p-aminohippuric acid on sodium thiosulfate determinations in renal clearance studies. *Bull. Johns Hopkins Hosp.*, 83: 213, 1948.
13. Berglund, H., Medes, G., Huber, G. C., Longcope, W. T. and Richards, A. N. The Kidney in Health and Disease, chap. v. Philadelphia, 1935. Lea & Febiger.
14. Harrison, E. H. Modification of the diphenylamine method for the determination of inulin. *Proc. Soc. Exper. Biol. & Med.*, 49: 111, 1942.
15. Chasis, H., Redish, J., Goldring, W., Ranges, H. and Smith, H. W. The use of sodium p-aminohippurate for the functional evaluation of the human kidney. *J. Clin. Investigation*, 24: 583, 1945.
16. Fisher, R. A. Statistical Methods for Research Workers. New York, 1950. Hafner Publishing Co.
17. Corcoran, A. C., Taylor, R. D. and Page, I. H. Functional patterns in renal disease. *Ann. Int. Med.*, 28: 560, 1948.
18. Bradley, S. E., Bradley, G. P., Tyson, C. J., Curry, J. S. and Blake, W. D. Renal function in renal diseases. *Am. J. Med.*, 9: 766, 1950.
19. Michie, A. J. and Michie, C. R. Unpublished data.
20. Michie, A. J., Michie, C. R. and Ragni, M. C. Kidney function in unilateral pyelonephritis. II. Physiologic interpretations. *Am. J. Med.*, 22: 190, 1957.
21. Mallory, G. K., Crane, A. R. and Edwards, J. E. Pathology of acute and of healed experimental pyelonephritis. *Arch. Path.*, 30: 330, 1940.
22. Sheehan, H. L. Medullary necrosis of the kidney. *Lancet*, 2: 187, 1937.

Kidney Function in Unilateral Pyelonephritis*

II. Physiologic Interpretations

ALEXANDER J. MICHIE, M.D., CATHARINE R. MICHIE, M.D. *and* MARIE C. RAGNI, B.A.
Philadelphia, Pennsylvania

IN the previous paper Michie and Michie[1] presented evidence indicating that chronic pyelonephritis may completely destroy small or large segments of renal tissue, leaving other segments essentially intact. The evidence indicates that damaged nephrons eventually become nonfunctional, or are repaired and operate in a normal manner. In unilateral pyelonephritis hypertrophy of nephrons in the non-diseased kidney and also of residual functional tissue in the diseased kidney tends to restore total renal function toward the normal level.[1,2] In this process the glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) in the diseased and non-diseased kidney maintain the same relationship to the residual functional tubular tissue, measured as Tm_{PAH}. This fact does not, however, exclude the possibility that both the diseased and contralateral kidneys may possess aberrant functional relationships as a result of the unilateral disease or of the hypertrophy. The following study was undertaken to examine this question by comparing the renal functional relationships found in patients with pyelonephritis with those reported in normal subjects.

METHODS

The patients reported here are the same as those cited in our previous paper,[1] where we also described the clinical methods and the renal clearance procedures. In order that the clinical history and basic data may be readily transferred from our previous report to this one, each kidney is identified by a unique symbol as shown in Figure 1.

Statistical Background Afforded by Normal Subjects. The primary features of renal function measured here (GFR, ERPF and Tm_{PAH}) have been summarized for normal subjects by Smith.[3] He also has made available a statistical analysis[3]† which permits the comparison of function in the diseased kidney with that of normal subjects in terms of the regression of any one function in relation to any other. The background parameters (Fig. 2)[3]‡ show the mean normal value, M, of the ratio GFR/Tm_{PAH}, with plus and minus twice the standard deviation, σ. The parameters (Fig. 3)[3]§ similarly show the mean normal value, M, plus and minus 2σ for the ratio $ERPF/Tm_{PAH}$. The ellipse (Figs. 2 and 3) represents the area within which 70 per cent of the observations on total renal function in normal subjects may be expected to fall by chance alone. If glomerular, tubular and vascular functions were affected equally by disease, the observations on the diseased kidneys would be expected to fall between the regression lines, $M \pm 2\sigma$, and to be equally distributed above and below the mean.

In unilateral studies in normal subjects each function would be reduced to approximately one-half the normal value, but without reduction of the relative magnitude of the standard deviation, that is, the coefficient of variation would remain the same. Thus by relating unilateral observations in pyelonephritis to the normal parameters we can examine the effects of disease on the non-diseased kidney as well as on the diseased organ.

For purpose of reference (Figs. 2 and 3) one-half the normal value[3]† for two kidneys may be taken as: GFR = 58.3 ± 14.1 ml./minute, ERPF = 320 ± 82 ml./minute, and Tm_{PAH} = 39.5 ± 6.6 mg./minute. All values are expressed per 1.73 $M.^2$ body surface area. In unilateral studies the normal values of the functional ratios‖ are expected to remain unchanged

† Smith,[3] page 545.
‡ Smith,[3] Figure 101.
§ Smith,[3] Figure 102.
‖ These means and standard deviations are taken from the table summarizing the data on mixed sexes (Smith[3] Table XII, pp. 544–545).

* From the Department of Physiology, New York University College of Medicine, the Harrison Department of Research Surgery of the Schools of Medicine of the University of Pennsylvania, the Urology Service of the Hospital of the University of Pennsylvania, and the Surgical Service of the Children's Hospital of Philadelphia. This study was financed by grants from the Dazian Foundation, the Commonwealth Fund, and the Harrison Department of Research Surgery of the Schools of Medicine of the University of Pennsylvania. A major portion of this work was done while the senior author was a National Research Council Fellow in the Medical Sciences in the Department of Physiology, New York University College of Medicine.

and are taken as: $GFR/Tm_{PAH} = 1.54 \pm 0.4$, $ERPF/Tm_{PAH} = 8.28 \pm 2.2$ and $GFR/ERPF = 18.2 \pm 4.0$.

The data obtained from diseased kidneys (Figs. 2, 3, and 4) are shown as symbols without protruding lines, data on the contralateral, non-diseased kidneys as symbols with protruding lines. Each symbol represents the average of three or more consecutive urine collection periods. Connected symbols indicate simultaneous determinations. Repeat examinations are plotted separately.

RESULTS

In order to compare the normal with the abnormal kidney, the variable functions must be related to a reasonably constant function of each kidney. While the filtration rate and renal blood flow are physiologically labile, Tm_{PAH} is stable. We also consider that Tm_{PAH} reflects the total quantity of functional proximal tubular tissue in the kidney. Accordingly, by expressing glomerular filtration and renal blood flow in terms of Tm_{PAH}, we can contrast the normal kidney with the pyelonephritic and with the non-diseased, usually hypertrophic, contralateral kidney.

Effects of Disease on Tm_{PAH}. In 84.8 per cent of thirty-three pyelonephritic kidneys, Tm_{PAH} was less than 39.5 mg./minute, one-half the normal value, and became negative in advanced disease. However a solitary pyelonephritic kidney in patient J. B. had supernormal function ($Tm_{PAH} = 66.5$ mg./minute).

In 86.7 per cent of fifteen non-diseased kidneys, Tm_{PAH} was greater than 39.5 mg./minute, half the normal value, and ranged up to 73.5 mg./minute in the single kidney of patient J. E. This unequal distribution of Tm_{PAH} conforms with the established fact that as the number of functional nephrons is reduced in the diseased kidney, compensatory hypertrophy occurs on the contralateral side.

Effects of Disease on the Filtration Rate. If pyelonephritis progressively destroys complete nephrons without selective action on the glomeruli and proximal tubules, it would be expected that the data obtained from the diseased kidney would follow the regression line M (Fig. 2) with equal scatter between the two regression lines indicated by $\pm 2\sigma$. Only three of thirty-five observations on the pyelonephritic kidneys with Tm_{PAH} greater than 10 mg./minute fall outside these parameters. But at the lowest levels of function the filtration rate tends to be preserved despite reduction in Tm_{PAH}. This phenomenon has been reported in other renal diseases and is attributed by Smith[3]* to the presence of "impotent" nephrons, that is, nephrons with functioning glomeruli attached to injured proximal tubules. Otherwise, the filtration rate was reduced roughly in proportion to Tm_{PAH}, although 70 per cent of the observations fell below the mean normal regression line. Consequently the GFR/Tm_{PAH} ratio for all pyelonephritic kidneys with Tm_{PAH} greater than 10 mg./minute averaged 1.36 ± 0.45 as compared with 1.54 ± 0.40 in normal subjects. This difference is not statistically significant ($t = 1.55$, $P < 0.2$).[4]

FIG. 1. Each kidney from each patient is represented by a separate symbol in order that the reader may recognize the basic data[1] from which the derived data were calculated.

* Smith,[3] page 606.

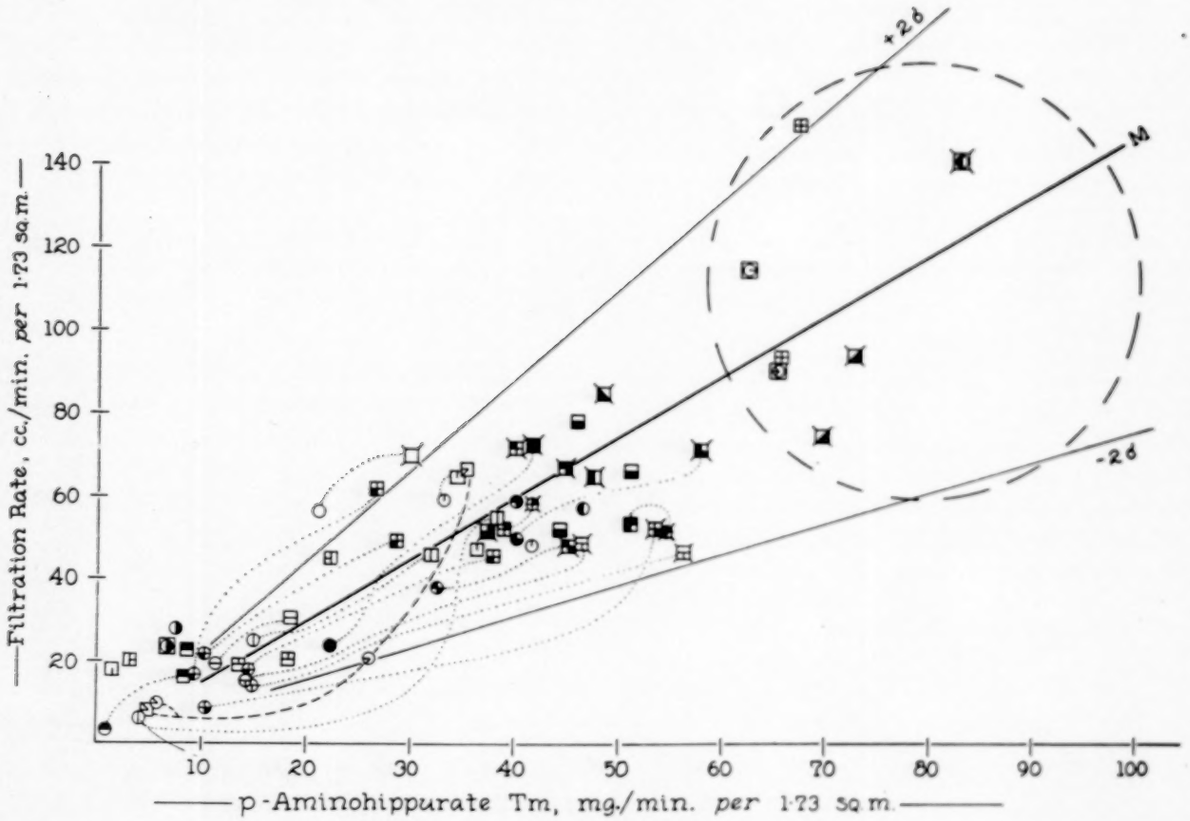


FIG. 2. Glomerular filtration rate related to Tm_{PAH}.

Correspondingly, if the increase in function of the non-diseased kidney tends to balance the functional deficit in the contralateral pyelonephritic kidney, the data obtained from the non-diseased kidney would be scattered evenly about the regression line M (Fig. 2) and would lie between the two regression lines indicated by $\pm 2\sigma$. In no instance did the GFR/Tm_{PAH} ratio of the non-diseased kidney fall outside the parameters $M \pm 2\sigma$. Nevertheless 73 per cent of these observations were below the normal mean of the GFR/Tm_{PAH} ratio. As a result the average GFR/Tm_{PAH} ratio for the non-diseased kidney is 1.32 ± 0.43. When this value is compared with the normal ratio of 1.54 ± 0.40, the difference is not statistically significant ($t = 1.705$, $P < 0.1$). Hence we conclude that the filtration rate increases in a parallel manner with proximal tubular function during compensatory hypertrophy.

Effects of Disease on Effective Renal Plasma Flow. Likewise, when ERPF was related to Tm_{PAH} and when Tm_{PAH} was greater than 10 mg./minute only two of thirty-five observations on the pyelonephritic kidney fell outside the parameters $M \pm 2\sigma$. (Fig. 3.) At lower values of Tm_{PAH} effective renal plasma flow was maintained at a relatively high level, that is, seven observations are above the $+2\sigma$ parameter. Smith (personal communication) believes that this "vicarious hyperemia" is due to diffusion of p-aminohippurate from inert to functioning nephrons or to capillary diversion of blood to functioning nephrons. Otherwise reduction in effective renal plasma flow, like that of glomerular filtration rate, was roughly proportional to the reduction in Tm_{PAH}. Because 83 per cent of the data on the diseased kidney (Fig. 3) fell between the mean and $M - 2\sigma$, the $ERPF/Tm_{PAH}$ ratio averaged $6.82 + 1.88$ for pyelonephritic kidneys having a Tm_{PAH} greater than 10 mg./minute. The difference between this mean, 6.82 ± 1.88, and the normal mean, 8.28 ± 2.2, is statistically significant ($t = 2.405$, $P < 0.02$)[4] and indicates a moderate degree of renal ischemia in the residual functional tissue of the pyelonephritic kidney.

Since 93 per cent of the observations on the non-diseased kidney lie below the normal mean, the average value of the $ERPF/Tm_{PAH}$ ratio for these kidneys, 6.35 ± 1.69, is slightly less

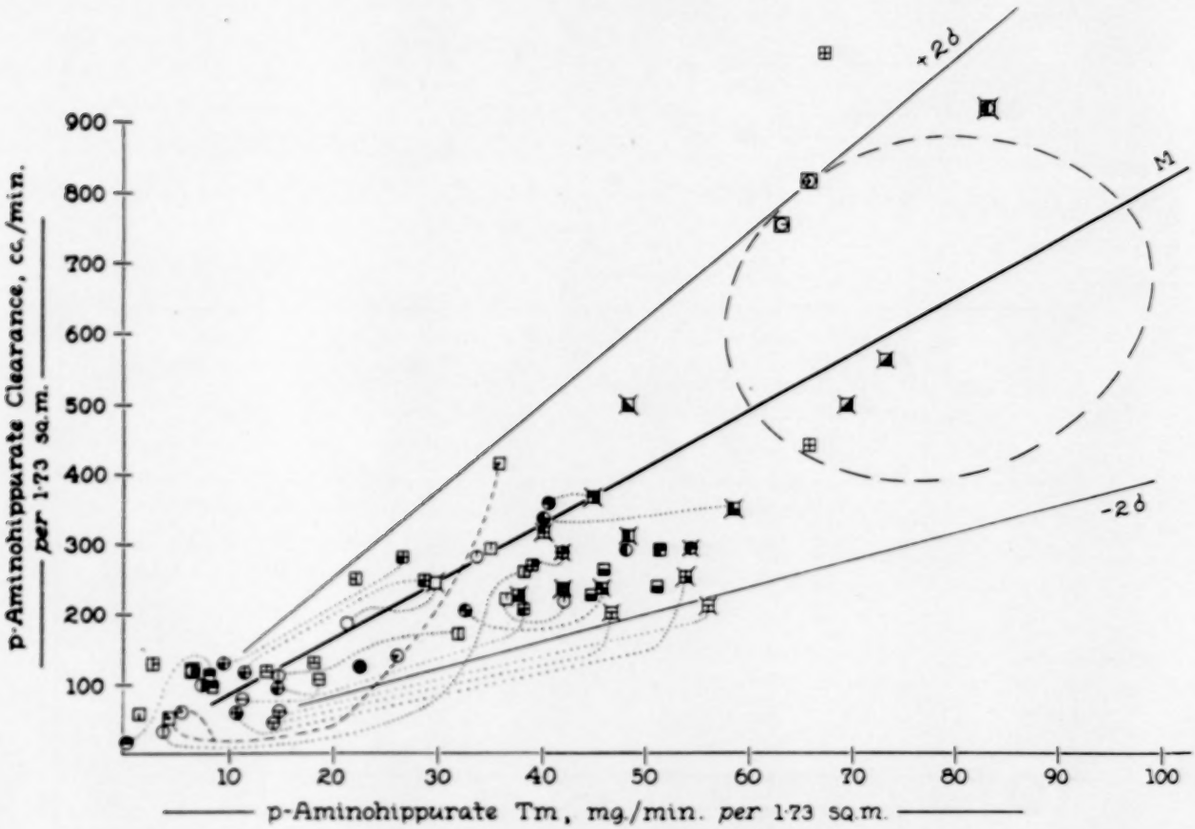


FIG. 3. Effective renal plasma flow related to Tm_{PAH}.

than that for the pyelonephritic kidney, 6.82 ± 1.88, and is significantly less than the normal value, 8.28 ± 2.2 ($t = 2.851$, $P < 0.01$).[4] Hence the ischemia (relative to residual functional tissue) which characterizes the pyelonephritic kidney also characterizes the hypertrophic contralateral kidney, although the degree of hypertrophy is not marked, that is, the average Tm_{PAH} for the group, 48.0 ± 9.1 mg./minute,[19] is only slightly larger than Tm_{PAH} for the normal kidney, 39.5 ± 6.6 mg./minute.

Effects of Disease on the Filtration Fraction. The relative magnitude of the changes in effective renal plasma flow and in filtration rate are reflected directly in the GFR/ERPF ratio or the filtration fraction. In a few subjects, (Fig. 4) this ratio was greater than the normal $M + 2\sigma$ parameter. Yet the distribution above and below the mean was so nearly symmetric that we infer that effective renal plasma flow and glomerular filtration rate usually tend to change in a parallel manner in both the pyelonephritic and the non-diseased contralateral kidney.

[19] Michie,[1] Table v.

Effects of Disease on Renal Conductance. At a fixed arterial pressure, the renal blood flow varies inversely with the total resistance, R, in the organ. However, as Gomez[5] pointed out, it is more convenient to think in terms of vascular conductance, the reciprocal of resistance, $\frac{1}{R}$. Total conductance decreases with progressive reduction of the renal vascular tree and approaches zero conductance at zero blood flow.

Inasmuch as chronic pyelonephritis destroys entire nephrons or gross portions of the kidney, it may also destroy the related vascular bed; in which case, Tm_{PAH} may reflect not only the quantity of functional tissue in the kidney but also the vascular supply to this functional tissue. In this view conductance should vary directly with Tm_{PAH} and should become zero when the entire kidney has been destroyed. The basic relation between conductance and Tm_{PAH} would be:

$$\frac{1}{R} \times \frac{1}{Tm_{PAH}} = \text{a constant}$$

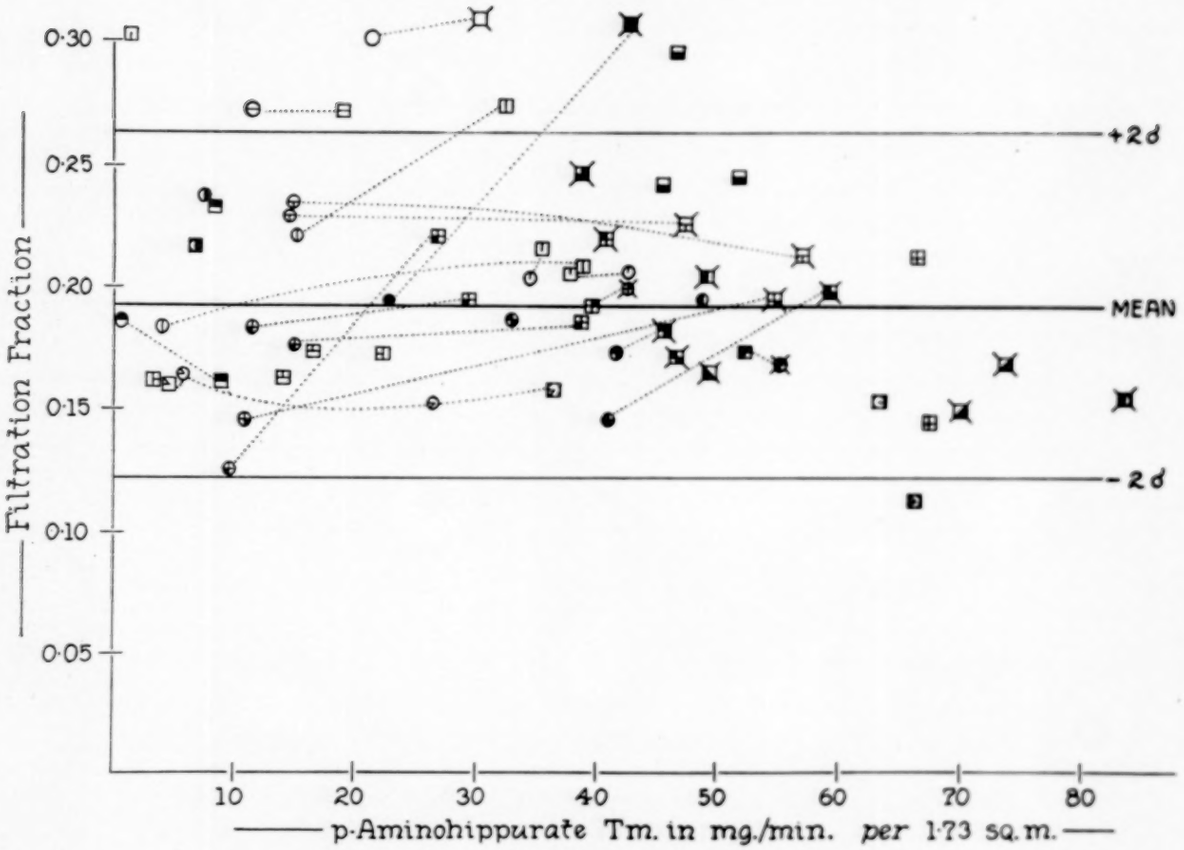


FIG. 4. The filtration fraction, GFR/ERPF related to Tm_{PAH}.

which expresses conductance in terms of Tm_{PAH}. In calculating the individual values (Table 1) we used Gomez's formulas.[3*,6] The conductance data for the normal kidney were calculated from the data of Bolomey et al.[7] As expected in theory, the values for $\frac{1}{R} \times \frac{1}{Tm_{PAH}}$ were fairly constant in spite of wide variations in Tm_{PAH} for both the pyelonephritic and the contralateral non-diseased kidney. There was no statistical difference in conductance, with respect to mean values, between the pyelonephritic and the non-diseased kidney, but there was a significant difference between these kidneys and the normal kidney. The reduction in conductance in the diseased and non-diseased kidney suggests that a common factor was operating to produce slight to moderate renal ischemia in both kidneys.

COMMENTS

The function of a solitary non-diseased kidney increases rapidly after unilateral nephrectomy and ultimately approaches the level of function of two normal kidneys.[5,9] Oliver[10] has shown in the rat that the number of glomeruli is not increased and that glomerular hypertrophy and tubular hyperplasia, especially of the proximal segment, occur in the hypertrophic kidney. From embryologic and anatomic considerations Smith[3*] concludes that during hypertrophy in man no new nephrons are formed and that the increased function is divided among pre-existing nephrons.

Our data show that in unilateral pyelonephritis, as a consequence of hypertrophy in the non-diseased kidney, the combined function of the two kidneys approaches that of two normal kidneys.[1] In the non-diseased kidney tubular function, as measured by Tm_{PAH}, and glomerular filtration increase roughly in a parallel manner in spite of a moderate ischemia indicated by the reduced value of effective renal plasma flow per unit Tm_{PAH}. In seeking a possible explanation for this fact it may be noted that, according to Gomez's hemodynamic analysis,[6]

* Smith,[3] page 583.

* Page 476.

TABLE I
RENAL CONDUCTANCES

Normal Kidneys			Non-diseased Kidneys			Pyelonephritic Kidneys		
Subject	$\frac{1}{R} \times \frac{1}{Tm_{PAH}}$	Tm_{PAH}	Patient	$\frac{1}{R} \times \frac{1}{Tm_{PAH}}$	Tm_{PAH}	Patient	$\frac{1}{R} \times \frac{1}{Tm_{PAH}}$	Tm_{PAH}
P. M.	0.129	1.103	K. C.	0.108	0.82	J. B.	0.087	1.11
M. S.	0.213	0.977	E. M.	0.107	0.71	D. F.	0.085	0.76
J. W.	0.168	1.250	K. K.	0.067	0.91	K. C.	0.101	0.82
N. W.	0.136	1.800	E. G.	0.218	0.41	M. S. (right)	0.077	0.25
T. K.	0.130	1.552	M. H.	0.058	0.85	M. S. (left)	0.071	0.65
J. S.	0.131	0.808	N. T.	0.076	0.77	N. T.	0.079	0.55
A. K.	0.120	1.065	E. M'.	0.077	0.92	E. M'.	0.081	0.87
E. K.	0.102	1.625	S. H.	0.136	0.76	M. H'.	0.089	0.31
S. W. C.	0.153	1.117	D. W.	0.091	0.71	R. K.	0.157	0.37
			M. R.	0.062	0.79	E. B. (right)	0.150	0.57
			J. E.	0.097	1.16	E. B. (left)	0.153	0.60
			M. G.	0.150	0.82	M. H.	0.131	0.39
						E. M.	0.107	0.67
						S. H.	0.141	0.68
						M. R.	0.062	0.24
						D. W.	0.088	0.38
						K. K.	0.071	0.17
(mean) 0.142 ± 0.032			(mean) 0.104 ± 0.046			(mean) 0.102 ± 0.032		
Comparison of the means: Normal			$P < 0.05$			$P < 0.01$		
Non-diseased			.....			$P < 0.9$		

Note: $\frac{1}{R} \times \frac{1}{Tm_{PAH}}$ is expressed in dynes^{-1} mg.$^{-1}$ cm.$^{5} \times 10^{-3}$ and Tm_{PAH} in mg. sec.$^{-1}$. In repeat examinations of the same kidney, only the results from the last experiment are used so that each kidney appears once. Data from kidneys with Tm_{PAH} values less than 10 mg./minute and from kidneys of hypertensive patients are omitted in this analysis.

an increase in renal interstitial pressure from the normal value of 10 to 20 mm. of mercury will not alter the filtration rate but will reduce effective renal plasma flow per unit Tm_{PAH} of the normal kidney to the level found in the non-diseased kidney. It is possible that nephron hypertrophy increases the renal volume within the relatively inelastic renal capsule and thus increases renal interstitial pressure.

The situation in the pyelonephritic kidney differs only in respect to the destruction of some fraction of the renal parenchyma. It is generally agreed[11–14] that the proportional regression of glomerular and tubular function reflects the destruction of entire nephrons. It may be supposed that this functional deficit leads to hypertrophy of the residual functional nephrons in the diseased as well as the non-diseased kidney. This inference is supported by the fact that, when the filtration rate and effective renal plasma flow are compared in terms of Tm_{PAH}, there is no measurable difference in the two sides.[6] The proportional increase in filtration rate and tubular function maintains glomerular-tubular balance in both organs; this balance is maintained in the pyelonephritic kidney as long as Tm_{PAH} is greater than 10 mg./minute.

Acute pyelonephritis is characterized by a variable degree of renal hyperemia.[15] In some patients the renal blood flow approaches values observed in pyrexial hyperemia.[16] In the first study on patient J. B. a moderate renal hyperemia was still present after two weeks of intensive sulfathiazole therapy. After prolonged anti-

bacterial therapy, the pyuria and bacilluria usually disappear and the hyperemia is replaced by a moderate ischemia which is comparable to that observed in the non-diseased kidney. A transition from the hyperemic to the ischemic phase was observed in patients M. S., D. F., J. M. (left) as well as in J. B. As already suggested the ischemia may be secondary to increased intrarenal pressure.

SUMMARY

The rate of glomerular filtration relative to the quantity of functioning tubular tissue, GFR/Tm_{PAH}, remains within the normal statistical limits in both the non-diseased and pyelonephritic kidneys as long as Tm_{PAH} is greater than 10 mg./minute. Thus glomerular-tubular balance is preserved.

Pyelonephritis provokes a functional deficit which in turn induces compensatory hypertrophy in the non-diseased kidney. It is inferred from anatomic and functional evidence that similar hypertrophy occurs in the residual functional nephrons in the diseased kidney.

Acute pyelonephritis, associated with fever and marked pyuria, is accompanied by renal hyperemia, that is, effective renal plasma flow per unit Tm_{PAH} is greater than the normal value. But chronic pyelonephritis not associated with fever or marked pyuria is characterized by a moderate ischemia in both the diseased and non-diseased kidney. It is suggested that this ischemia may be secondary to an increase in intrarenal pressure, the increase being caused by parenchymal hypertrophy within the relatively inelastic fibrous capsule.

Acknowledgment: The authors are grateful to Dr. Homer W. Smith for his stimulating encouragement.

REFERENCES

1. Michie, A. J. and Michie, C. R. Kidney function in unilateral pyelonephritis. I. Clinical data. *Am. J. Med.*, 22: 179, 1957.
2. Hinman, F. The condition of renal counterbalance and the theory of renal atrophy of disuse. *J. Urol.*, 49: 392, 1943.
3. Smith, H. W. The Kidney, Structure and Function in Health and Disease. New York, 1951. Oxford University Press.
4. Fisher, R. A. Statistical Methods for Research Workers. New York, 1950. Hafner Publishing Co.
5. Gomez, D. M. Hemodynamique et Angio Cinétique. Paris, 1941. Hermann et Cie.
6. Gomez, D. M. L'hemodynamique de la circulation renale. *Rev. Sc.*, 85: 451, 1947; Idem. Evaluation of renal resistances. *J. Clin. Investigation*, 30: 1143, 1951.
7. Bolomey, A. A., Michie, A. J., Michie, C. R., Breed, E. S., Schreiner, G. E. and Lauson, H. D. Simultaneous measurement of effective renal blood flow and cardiac output in resting normal subjects and patients with essential hypertension. *J. Clin. Investigation*, 38: 10, 1949.
8. Weiss, E. and Chasis, H. Failure of nephrectomy to influence hypertension in unilateral kidney disease. *J. A. M. A.*, 123: 277, 1943.
9. Welsh, C. A., Wellen, I., Taylor, H. C. and Rosenthal, A. Changes in renal function accompanying the hypertrophy of the remaining kidney after unilateral nephrectomy. *J. Clin. Investigation*, 23: 750, 1944.
10. Oliver, J. New directions in renal morphology: a method, its results, and its future. *Harvey Lect.*, 40: 102, 1944, 1945.
11. Bradley, S. E., Bradley, G. P., Tyson, C. J., Curry, J. J. and Blake, W. D. Renal function in renal diseases. *Am. J. Med.*, 9: 766, 1950.
12. Corcoran, A. C., Taylor, R. D. and Page, I. H. Functional patterns in renal disease. *Ann. Int. Med.*, 28: 560, 1948.
13. Raaschou, F. Studies of Chronic Pyelonephritis. Copenhagen, 1948. Ejnar Munksgaard.
14. Cargill, W. H. The measurement of glomerular and tubular plasma flow in the normal and diseased human kidney. *J. Clin. Investigation*, 28: 533, 1949.
15. Michie, A. J. Unpublished data.
16. Bradley, S. E., Chasis, H., Goldring, W. and Smith, H. W. Hemodynamic alterations in normotensive and hypertensive subjects during the pyrogenic reaction. *J. Clin. Investigation*, 24: 749, 1945.

The Valsalva Maneuver as a Test of Cardiac Function*

Pathologic Physiology and Clinical Significance

RICHARD GORLIN, M.D.,† JOHN H. KNOWLES, M.D. *and*
CAPTAIN CLIFFORD F. STOREY, M.C., U.S.N. (Ret.)
Portsmouth, Virginia

ALTHOUGH Derbes and Kerr[1] have pointed out that Weber and not Valsalva first described the circulatory effects of airway straining, the authors have chosen to use the more popular phrase "Valsalva maneuver" in this paper.

Study of the changes in blood pressure caused by forced airway straining has frequently been advocated as a test of vasomotor control of the circulation.[2–6] Interest has usually centered on the overshoot in arterial pressure which follows the period of increased airway pressure. This overshoot presumably depends on hypotension developing during straining and mainly represents the effects of reflex vasoconstriction.[7] On the other hand, whether or not blood pressure does decrease during straining seems to depend on function of the heart itself. This phenomenon not only poses an intriguing physiologic problem as to its origin but also provides the basis for a simple bedside test in the diagnosis of cardiac disease.[8] This report will attempt to demonstrate further the pathologic physiology and clinical significance of the various blood pressure responses to airway straining, particularly in disease of the left side of the heart.

Hamilton[9] was the first to observe that during the straining phase of Valsalva's maneuver arterial pressure remained unchanged in patients with congestive failure instead of decreasing precipitously as in the normal. (Fig. 1.) Greene and Bunnell described a sustained arterial pressure response in some cases of mitral stenosis.[10] Price and Connor noted a similar finding in three cases of chronic constrictive pericarditis.[11] Lee, Matthews and Sharpey-Schafer[12] reported on the central circulatory changes in normal individuals during the Valsalva maneuver and Judson et al.[13,14] described changes in pulmonary arterial pressure and circulation time in patients with both normal and abnormal responses. Sharpey-Schafer[15] presented a large group of patients with failing hearts who showed an abnormal peripheral arterial pressure response and alluded to the clinical value of the maneuver.

MATERIAL AND METHODS

The following seventy-eight patients were studied: Seven normal subjects, seven patients with pulmonary parenchymal disease, three with pulmonic stenosis, three with atrial septal defect, nineteen with mitral stenosis, twenty-seven with left ventricular disease due to aortic stenosis and/or insufficiency, hypertension or coronary disease, two with chronic constrictive pericarditis, seven with bilateral congestive failure, three with apparently pure right ventricular disease. (Table 1.) Each patient was classified as to disability according to the criteria of the American Heart Association.[16]

Forced expiration from the inspiratory mid-position was performed against an aneroid manometer to a pressure of 40 mm. of mercury and held ten to twelve seconds. The maneuver was done with the patient in the recumbent position and then with the patient on the tilt table with the head or the legs elevated 30 degrees. Both directly recorded and ausculted arterial blood pressures were measured in all patients. Arm to tongue decholin® circulation time, vital capacity and venous pressures were measured. The effects of the Valsalva maneuver on pulmonary capillary wedge,[17] pulmonary arterial, right atrial, inferior vena caval

* From the Cardiopulmonary Function Laboratory, U. S. Naval Hospital, Portsmouth, Virginia. The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or of the naval service at large.

† Present address: Boston, Massachusetts.

TABLE I

VALSALVA RESPONSES IN SEVENTY-EIGHT PATIENTS

Condition	Name	Age (yr.)	Cardiac Class	Pressures (mm. Hg)		Comment
				Pulmonary Wedge	Right Atrial	
			Normal Valsalva Response			
Normal	D. B.	19	0	10	7	Basal systolic murmur
	R. W.	22	0	9	4	Apical systolic murmur
	D. M.	19	0	7	1	Idiopathic clubbing
	E. T.	22	0	7	3	Basal systolic murmur
	R. B.	23	0	10	0	Basal systolic murmur
	D. S.	19	0	5	4	Basal systolic murmur
	W. Z.	21	0	7	0	Right bundle branch block
Pulmonic stenosis, mild	M. V.	23	0	5	3	Calculated pulmonary valve area = 1.2 cm.^{2}
	B. B.	17	0	7	4	Calculated pulmonary valve area = 1.6 cm.^{2}
	D. H.	20	0	11	6	Calculated pulmonary valve area = 1.7 cm.^{2}
Mitral stenosis, mild	R. M.	24	0	.....	*6*	Murmur only
	E. G.	31	I	.....	*4*	Murmur only
	B. W.	25	I	7 (10)	2	Murmur only
	L. K.	34	II	17	6	Mitral valve area = 1.5 cm.^{2}
Left ventricular disease: Mitral insufficiency	M. S. L.	24	I	9	0	Left atrium 1+ enlarged; pulmonary wedge = mitral insufficiency wave form
	C. C.	42	II	7	6	Left atrium 2+ enlarged; pulmonary wedge = mitral insufficiency wave form
	M. D.	39	II	.....	*5*	After digitalization: left atrium 2+ enlarged
	B. S.	26	II	10 (15)	5	Following digitalization: left atrium 2+ enlarged
Aortic stenosis	W. M.	67	II	.....	*6*	Electrocardiogram and x-ray normal; arterial contour abnormal
	H. C.	37	I	8 (8)	0 (2)	No symptoms; x-ray, electrocardiogram and hemodynamics normal; arterial contour abnormal
Aortic insufficiency	E. R.	30	I	.....	*10*	Blood pressure 150/30
	N. M.	37	I	.....	*8*	Blood pressure, 138/60
	E. P.	47	I	.....	*8*	Blood pressure, 140/65
	Hi. C.*	32	II	6 (10)	1	After digitalization; blood pressure, 140/50
Aortic coarctation	G. B.*	20	I	.....	5	Postresection; blood pressure, 140/80
Coronary artery disease						After digitalization for myocardial infarction with shock:
	A. B.	49	II	.....	*6*	blood pressure, 120/80
	J. P.	37	II	.....	*6*	blood pressure, 130/85
Hypertension	P. L.	23	II	.....	8	Blood pressure, 160/100
	P. F.	51	I	.....	5	Blood pressure, 220/120
Postpericardiectomy (6 weeks)	J. E.	24	I	6	3	.....
Atrial septal defect	H. C.	51	III	3	3	Pulmonary hypertension, nil shunt
	B. T.	24	I	10	8	Pulmonary flow, 6.9; syst. = 2.9 L./min./M.^{2}
	H. Y.	19	I	10	9	Pulmonary flow, 11.5; syst. = 2.5 L./min./M.^{2}

Note: Data in italics signify peripheral venous pressure. Figures in ( ) represent measurements during exercise.

* Patients showing changed Valsalva response after therapy.

TABLE 1 (*Continued*)

VALSALVA RESPONSES IN SEVENTY-EIGHT PATIENTS

Condition	Name	Age (yr.)	Cardiac Class	Pressures (mm. Hg)		Comment
				Pulmonary Wedge	Right Atrial	
Right ventricular disease: Pulmonary hypertension	F. C.	38	II	7	4 (8)	Pulmonary artery mean pressure, 70 mm. Hg
Differential diagnosis of dyspnea	E. Sch.	60	III	.....	*Normal*	Emphysema
	H. H.	21	III	.....	*Normal*	Asthma
	R. T.	72	III	.....	*Normal*	Emphysema vs. congestive failure
	B. D.	50	II	.....	*Normal*	Obesity and pulmonary fibrosis vs. congestive failure
	B. I.	26	II	.....	*Normal*	Pulmonary fibrosis
	H. S.	49	IV	.....	*Normal*	Tuberculosis
	T. G.	63	II	.....	*Normal*	Emphysema vs. congestive failure
	P. C.	35	I+	.....	*Normal*	Obesity and thyrotoxicosis vs. congestive failure
Intermediate Valsalva Response						
Mitral stenosis	R. K.	34	II	.....	*8*	Postcommissurotomy
	E. W.	23	II	15 (38)	4	Mitral valve area = 1.2 cm.² (calculated, measured)
	S. W.	18	II	.....	*5*	.....
	J. D.	32	II	23	4	Mitral valve area = 1.2 cm.² (calculated, measured)
	H. W.*	22	II	.....	*8*	Mitral valve area = 1.4 cm.² (measured)
	I. D.	22	II+	.....	*8*	.....
	C. A.*	35	II	17	4	Mitral valve area = 1.4 cm.² (calculated, measured)
	E. D.	27	II	.....	*4*	.....
	E. L.	18	III	.....	*8*	4 mo. pregnant
	S. I.	26	II+	11 (20)	2	Mitral valve area = 1.6 cm.² (calculated); high output
	O. S.	50	III	18 (34)	5	Mitral valve area = 0.9 cm.² (calculated, measured)
	N. R.*	22	II	.....	*5*	Postcommissurotomy and postpartum; mitral valve area = 1.2 cm.² (measured) (BS area = 1.3)
Left ventricular failure: Mitral insufficiency	M. D.*	39	II	20	4	Before digitalization
	C. G.	37	II	.....	*8*	.....
Aortic stenosis	R. R.	8	I	.....	*6*	.....
	J. Bo.	60	III	.....	*7*	Left ventricular hypertrophy, syncope, angina
	C. D.	25	II+	14 (40)	2	Left ventricular hypertrophy, fatigue, edema
	R. J.	20	I	.....	*8*	No symptoms
Aortic insufficiency	J. Br.	20	II	12 (18)	3 (4)	Blood pressure, 150/40; digitalized
	L. L.	23	I	.....	*7*	Blood pressure, 135/45
	Hi. C.*	32	II+	.....	*8*	Blood pressure, 145/50; undigitalized
	F. A.	27	I	14 (22)	2 (3)	Blood pressure, 135/40
Aortic coarctation	G. B.*	20	I	.....	*6*	Blood pressure, 180/110

TABLE 1 (*Continued*)
VALSALVA RESPONSES IN SEVENTY-EIGHT PATIENTS

Condition	Name	Age (yr.)	Cardiac Class	Pressures (mm. Hg)		Comment
				Pulmonary Wedge	Right Atrial	
Coronary artery disease	P. S.	67	III	.....	*5*	Angina pectoris occurred following seven Valsalva tests
Right ventricular failure: Cor pulmonale	A. S.	56	IV	.....	*14*	Symptoms related to primary pulmonary disease
Combined ventricular failure: Myocardial disease ? cause	M. S *	64	III	.....	*10*	Postdiuresis
			Abnormal Valsalva Response			
Mitral stenosis	G. S.	38	III	.....	*13*	.....
	H. W.*	22	III	.....	*7*	Mitral valve area = 0.8 cm.² (measured)
	L. K.*	34	III	30	6	Mitral valve area = 0.9 cm.² (calculated, measured)
	N. R.*	22	III	.....	*12*	Mitral valve area = 0.8 cm.² (measured)
	E. S.	36	IV	22	18	.....
	A. C.	32	IV	.....	*10*	Mitral valve area = 0.5 cm.² (measured)
	C. A.*	35	II+	20	9	Mitral valve area = 0.8 cm.² (calculated, measured)
Left ventricular failure: Mitral insufficiency	P. D.	22	II+	30	4	.....
	S. B.	19	II	20	3	.....
Aortic stenosis	L. G.	21	II+	.....	*4*	Symptoms during pregnancy
Coronary artery disease	A. B.*	49	III	.....	*5*	Clinical shock: blood pressure, 85/70
	J. P.*	37	IV	.....	*10*	Blood pressure, 80/70
	T. H.	31	III	37	10	Acute onset dyspnea 10 days before
Right ventricular failure: Cor pulmonale	E. N. S.	53	IV	?15	20	Cor pulmonale with hypoxia, pulmonary artery mean pressure, 60
Combined ventricular failure: Any etiology	M. S.*	64	IV	.....	*12*	.....
	O. B.	65	IV	.....	*13*	.....
	H. C.	68	IV	.....	*14*	.....
	T. M.	44	IV	17	11	.....
	K. S.	52	IV	25	20	.....
	S. A.	44	IV	22	8	Mitral valve area = 1.6 cm.² mitral insufficiency associated
	G. W.	29	IV	28	14	.....
Pericardial constriction	J. E.*	24	IV	20	20	Before surgery
	J. E.*	24	IV	20	20	10 days postpericardiectomy
	J. B.	49	IV	23	22	Calcified pericardium

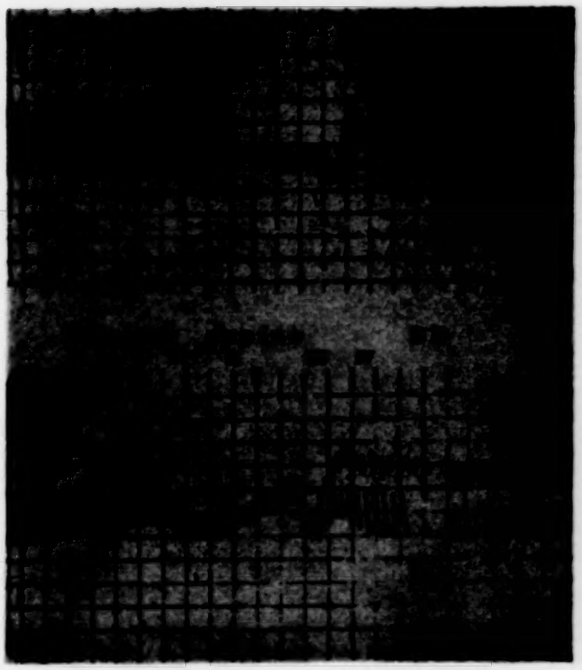


FIG. 1. Systemic arterial pressure in phases I through IV of the Valsalva maneuver, as described in the text. Upper graph, patient in standing position; lower graph, patient in supine position.

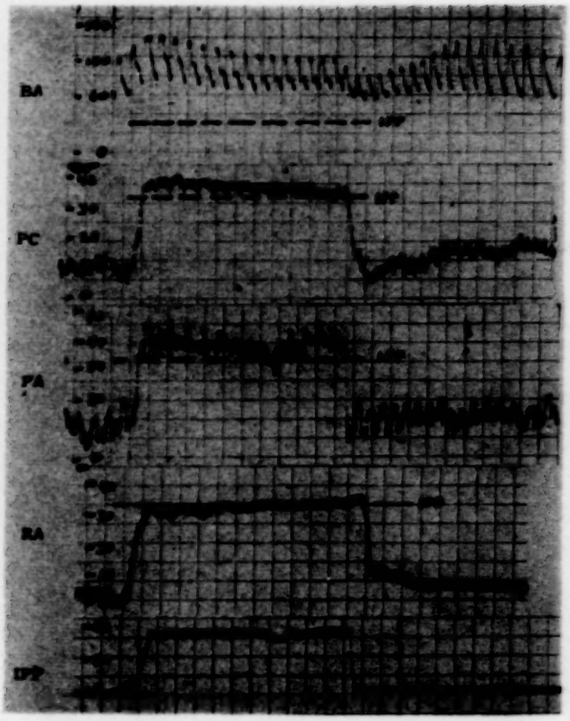


FIG. 2. Effect of normal ventricular function on the Valsalva response. Pulmonary wedge (PC), pulmonary artery (PA) and right atrial (RA) pressures were recorded during separate Valsalva maneuvers each with simultaneously recorded brachial arterial (BA) and airway or intrapulmonary (IPP) pressures. IPP has been drawn on each pressure record at the appropriate height; the pressure above this line represents effective pressure during airway straining. Note as BA pressure falls, PC falls to virtually zero effective pressure. PA does likewise but shows a secondary rise. RA started at about zero effective pressure and rose toward end of maneuver. PC overshoot is simultaneous with BA overshoot. A delay in decholin circulation time from RA to tongue was observed during straining.

and brachial venous pressures were recorded during cardiac catheterization in forty-two patients who represented each of the diseases and various types of response. Decholin circulation times from inferior vena cava, right atrium and pulmonary artery to tongue, were measured before, during and immediately following straining. (Table II.)

Airway or intrapulmonary pressure during straining was shown to approximate closely intraesophageal pressure in twelve patients.[18] Therefore this pressure was subtracted from pulmonary capillary wedge and right atrial pressures to obtain the effective left and right atrial pressures, respectively, during straining. The zero point for all pressures was 10 cm. anterior to the back. The pressures were recorded with Sanborn electromanometers or Statham strain gages.

RESULTS

Normal Response

Pressure and Flows. The normal systemic arterial pressure response, conveniently divided into four phases, is shown in Figure 1. The systolic pressure rose immediately with the onset of increased airway pressure following which systolic and pulse pressures fell very quickly to low values (phase I). The portion of the curve from the lowest point on is known as phase II. During this phase the mean arterial pressure began to rise although the pulse pressure remained narrowed. Following release of the strain (phase III) a rebound occurred in both systolic and pulse pressures, the overshoot (phase IV); this in turn was followed by a reflex bradycardia.[4–6] This pattern was altered only slightly by position. (Fig. 1.) Elevation of the legs caused a delay not exceeding one to two seconds in the phase I fall-off in pressure. Elevation of the head reduced the over-all pulse pressure without altering other characteristics. Abdominal compression likewise had little effect on the pattern of the normal response.[19]

Pulmonary arterial pressure showed a similar decrease in mean and pulse pressures and sometimes a late rise in mean pressure during phase II. (Fig. 2.) Effective pulmonary capillary pres-

TABLE II

THE EFFECT OF VALSALVA MANEUVER UPON THE DECHOLIN CIRCULATION TIME

Patient	Diagnosis	Valsalva Response	I.V.C. to Tongue: Control (in sec.)	I.V.C. to Tongue: Valsalva (in sec.)	P. A. (R. A.*) to Tongue: Control (in sec.)	P. A. (R. A.*) to Tongue: Valsalva: During (in sec.)	P. A. (R. A.*) to Tongue: Valsalva: After (in sec.)
D. M.	Normal	Normal	13	26	.....	.....	....
D. S.	Normal	Normal	11	17	.....	.....	....
K. W.	Normal	Normal	17	31	.....	.....	....
M. V.	P. S., mild	Normal	13.5	22.5	.....	.....	...
E. T.	Normal	Normal	....	....	8.5	11.5	5
N. C.	Normal	Normal	....	....	8.5	14	....
					10.5*	18*	....
M. S.	M. I.	Normal	....	....	10	14	6
C. C.	M. I.	Normal	....	....	9	14	....
B. S.	M. I.	Normal	....	....	11*	14*	....
W. F.	Normal	Normal	10	14	9	12	7
		Left-Sided Lesion Only					
M. D.	M. I. (L. V. F.)	Intermediate	12	18	10.5*	15*	9*
J. D.	M. S.	Intermediate	21	34	12	16.5	8
E. W.	M. S.	Intermediate	....	....	8	10.5	5.5
D. A.	A. S., A. I.	Intermediate	....	....	7.5	11	....
O. S.	M. S.	Intermediate	15	19.5	12*	15*	....
S. I.	M. S.	Intermediate	....	....	11*	14*	8*
P. D.	M. I. (L. V. F.)	Abnormal	25	32	13	17	....
S. B.	M. I. (L. V. F.)	Abnormal	....	....	17*	22*	13*
J. Br.	A. I. (L. V. F.)	Intermediate	....	....	13*	16.5*	....
T. H.	L. V. F.	Abnormal	....	....	20*	23.5*	....
		Right-Sided Lesion (with or without Left-Sided Lesion)					
C. A.	M. S. (with R. V. F.)	Abnormal	18	23	10.5	12	....
T. M.	C. V. F.	Abnormal	19.5	27.5	.....	.....	....
K. S.	C. V. F.	Abnormal	28	27	28	28	....
S. A.	C. V. F.	Abnormal	30	31	21	22	20
E. N. S.	R. V. F.	Abnormal	22.5	27	12	13	....
J. B.	C. V. F.	Abnormal	28	34	16*	16*	....
			27	32			

Note: I. V. C. = Inferior vena cava; P. A. = Pulmonary artery; R. A. = Right atrium; P. S. = Pulmonic stenosis; M. I. = Mitral insufficiency; M. S. = Mitral stenosis; L. V. F. = Left ventricular failure; R. V. F. = Right ventricular failure; and C. V. F. = Combined ventricular failure.

sure decreased during straining, usually approaching the level of intrapulmonary pressure or zero mm. Hg effective pressure. Rarely, a secondary rise in this pressure was seen in phase II. Effective right atrial pressure showed inconstant changes in the first one to two seconds but most often levelled off equal to intrapulmonary pressure. After eight seconds or more of straining, however, atrial pressure rose 2 to 5 mm. Hg above intrapulmonary pressure (or zero effective pressure). Inferior vena caval pressure was equal to or exceeded right atrial pressure by 3 mm. Hg in most patients as the result of abdominal straining.[3] The brachial venous pressure rose gradually but progressively to a plateau equalling the level of intrathoracic pressure.[20]

Decholin circulation time from inferior vena cava to tongue and from the right side of the

heart to tongue were both prolonged (during straining) three to fourteen seconds greater than the control. (Table II.) In three patients decholin was introduced into the pulmonary artery simultaneously with the release of the strain phase. Acceleration of blood flow during the overshoot phase was seen. (Table II.)

Correlations. There were no abnormalities in vital capacity, circulation time, heart size, pulmonary plethora, or right atrial pressure. Pulmonary capillary wedge pressure was slightly elevated in one patient with mild mitral stenosis. A normal response was seen in pregnant women, pulmonary parenchymal disease without cor pulmonale and in mild forms of heart disease.

Abnormal Response

Pressure and Flows. Systemic arterial systolic and pulse pressures rose with the onset of the airway strain and remained elevated with little change for at least six seconds and usually throughout phases I and II. (Figs. 3 and 5.) Following release of the airway pressure an overshoot was only rarely observed. Change in position had no effect on the abnormal response in this group of patients.

Two different patterns of response of the intrathoracic circulation were seen during the Valsalva maneuver. When there was a left-sided lesion only, like mitral stenosis or left ventricular failure (Fig. 3), the effective pulmonary capillary wedge pressure initially was 5 mm. Hg more or less than the resting level and then decreased at a variable rate during the period of straining. Similar falls were seen in pulmonary arterial pulse and mean pressure. The change in effective right atrial mean pressure was similar to the normal. (Figs. 3 and 4.) There was a delay in the circulation time to the tongue both from inferior vena cava and from the right side of the heart in these patients. (Table II.)

When there was a right-sided lesion such as isolated or combined right ventricular failure, there was little or no fall in effective pulmonary wedge or pulmonary arterial pressures during the maneuver. (Fig. 5.) In some the effective right atrial pressure decreased slightly, but usually this pressure was unchanged at values equal to or occasionally less than resting pressure. In four patients, T. M., C. A., T. B. and E. N. S., there was a delay in circulation time from inferior vena cava to tongue during the maneuver. In patients K. S. and S. A., however, there was little or no retardation of blood flow from the

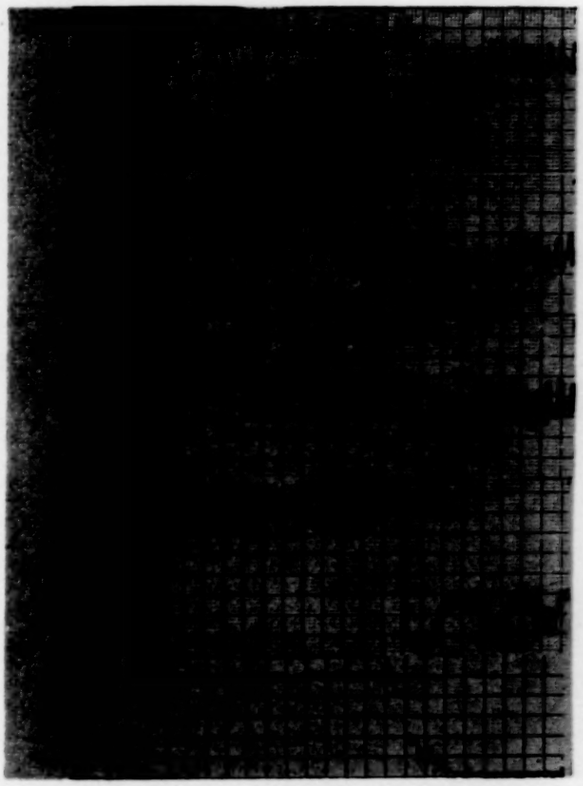


FIG. 3. Effect of abnormal left ventricular function on the Valsalva response. Method and symbols are the same as in Figure 2. Note the sustained BA pressure while effective PC and PA pressures (pulse and mean) are falling to levels lower than control pressures, but still abnormally elevated. Effective RA pressure was less than the control throughout and there was a delay in decholin circulation time from RA to tongue during straining.

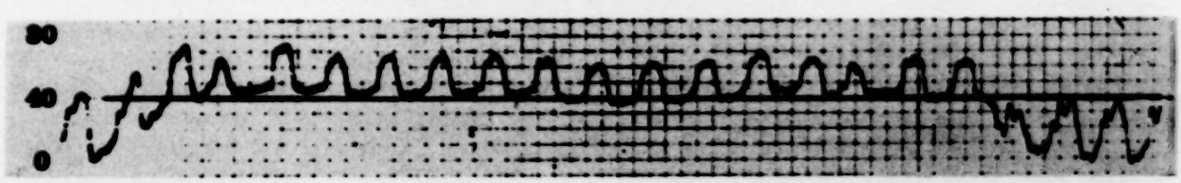


FIG. 4. Normal right ventricular function during abnormal Valsalva response. Note the falling right ventricular diastolic pressure up to the ninth beat with a decreased pulse pressure. This is followed by a rising diastolic and pulse pressure to the end of straining. The Valsalva response was abnormal yet circulation time from RA to tongue was prolonged during the maneuver.

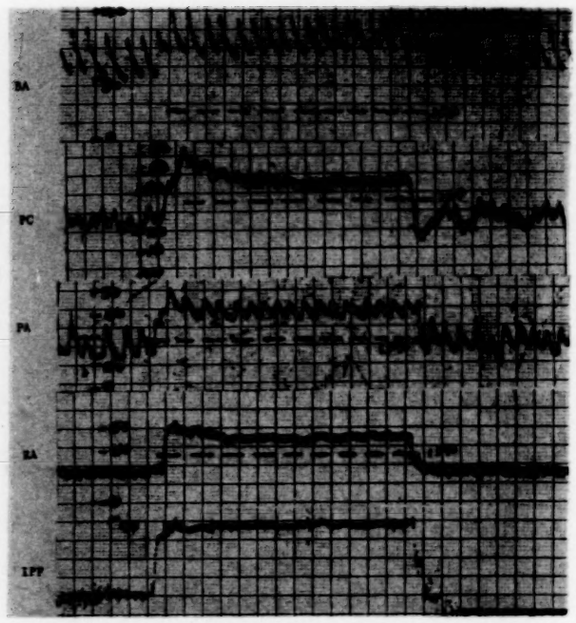


FIG. 5. Effect of abnormal right and left ventricular function on the Valsalva response. Method and symbols are the same as in Figure 2. After an initial spike in pressure, effective PC, PA and RA pressures all reach a plateau which persists during straining. PC and RA pressures are also at lower effective levels than control values yet BA pressure is sustained. PA pulse pressure likewise remains virtually unchanged although smaller and at a lower effective pressure.

abdomen with airway pressures of 30 mm. of mercury. All patients with a right-sided lesion had virtually unchanged intrathoracic circulation times during the maneuver. (Table II.)

Correlations. Figure 6 indicates there was a good correlation between an abnormal arterial pressure response and other tests of circulatory function. Either pulmonary capillary wedge or right atrial pressure, or both were increased at rest in all patients with an abnormal response. (Fig. 6.) Nineteen of twenty-three patients were class III or IV cardiac patients.

An abnormal test was seen in tight mitral stenosis (calculated or measured valve area equal to 1 $cm.^2$ or less), tight aortic stenosis (estimated valve area 0.5 $cm.^2$), left ventricular failure with pulmonary congestion, right ventricular failure and chronic constrictive pericarditis.

Intermediate Response

Pressures and Flows. There were three variations in arterial pressure response between the normal and abnormal types. (1) Twelve patients with mild valvular disease or ventricular failure showed a striking alteration in the Valsalva response with change in position. (Fig. 7.) When the test was done in the head up position on the tilt table all results were normal. When placed in the horizontal position, five became abnormal (pulse and systolic pressure remaining elevated for four seconds or more). When the legs were elevated, the remaining seven patients also showed an abnormal response. Exercise and vigorous inspiratory effort induced an abnormal response in half of the patients who responded normally in the resting supine position. (2) In three patients repeated Valsalva tests resulted in a progressively more abnormal response. (3) Six patients showed a fall in systolic pressure of less than 10 mm. Hg with an unchanged pulse pressure during straining. These three groups of patients were considered together as having an intermediate response.

The pulmonary capillary wedge pressure decreased during straining. The effect of position on rate of fall of pressure and arterial pressure response are shown in Figure 8. Pulmonary arterial and right atrial pressures showed changes similar to the normal with sharper decreases in pressure with change in position.

Correlations. There was correlation of the Valsalva response with the fluoroscopic appearance of minimal pulmonary congestion in fifteen of twenty-six patients. Twenty-five patients had some form of heart disease involving either left ventricle or mitral valve and most were class II cardiac patients. Only scattered abnormalities were seen in other tests of cardiac function. (Fig. 6.) Pulmonary wedge pressure was elevated or borderline in the nine patients in whom it was measured and rose in all nine on effort. Central or brachial venous pressure was normal in twenty-five of twenty-six. Patient A. S. with severe cor pulmonale due to pulmonary disease, had a venous pressure of 14 mm. Hg and a circulation time of fifty-six seconds.

An intermediate response was seen with moderate mitral stenosis (1 to 1.5 $cm.^2$), left ventricular failure due to mitral insufficiency, aortic stenosis with or without insufficiency, coarctation of the aorta, or coronary artery disease, and with pure right ventricular failure.

Effects of Specific Therapy

Effective cardiac therapy usually resulted in a change in the Valsalva maneuver response. Effects of mitral commissurotomy were observed in patients H. W., L. K., C. A. and N. R. Near

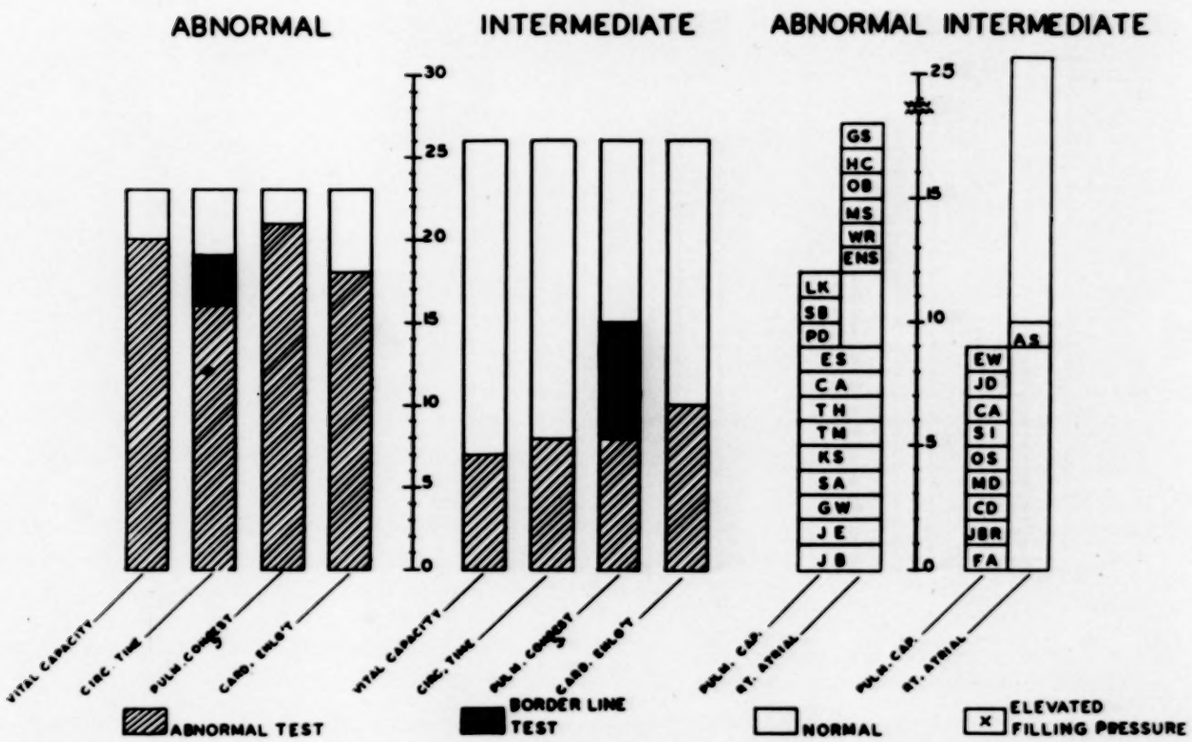


FIG. 6. Correlation of other tests of circulatory function with the Valsalva response. On the left are shown the number of patients in each category with abnormal circulatory function tests. In the columns on the right are shown the patients in whom pulmonary capillary or central venous pressure was abnormal. When the block extends across both columns, both pressures were measured; the initials appear only when a pressure value was abnormally elevated at rest or on mild effort.

doubling of the valve area from 0.8 to 1.5 cm.^{2} in H. W. changed the response from abnormal to an intermediate. (Fig. 9A.) In patient N. R. commissurotomy was performed in the fifth month of pregnancy. Despite an increase in estimated valve area from 0.5 to 1.2 cm,^{2} the patient's symptoms persisted and the Valsalva response remained abnormal. Following delivery when cardiac output and valve gradient were decreased,[21,22] symptoms disappeared and the Valsalva response became normal. (Fig. 9B.) The effect of pericardiectomy was shown in patient J. E. (Fig. 10.) Prior to operation pulmonary and systemic venous pressures were elevated, circulation time prolonged and the response abnormal. This abnormal response persisted one week after successful operation in association with elevated pulmonary and peripheral venous pressures. A small overshoot not formerly present, however, was seen in phase IV and there was a concomitant decrease in circulation time. Six weeks after operation with loss of edema fluid and return of pulmonary and systemic venous pressures to normal, the Valsalva response also became normal. (Fig. 10.) Digitalization resulted in conversion to a normal response in patients M. D., Hi. C., A. B. and J. P. In patient M. S. vigorous successful diuresis resulted in conversion of an abnormal to an intermediate response.

METHODS OF DETECTION OF ARTERIAL PRESSURE RESPONSE

In about 80 per cent of the patients it was possible to detect the change denoted on the direct arterial tracing by means of a blood pressure cuff. In 20 per cent where the fall in systolic pressure was delayed or atrial fibrillation was present, a direct tracing was necessary.

COMMENTS

Normal Response. In order to understand the causes of the abnormal response it is necessary first to understand the mechanism of production of the normal arterial response to the Valsalva maneuver. Sarnoff, Berglund and Case have carefully reinvestigated Starling's law of the heart.[23,24] They have demonstrated that the

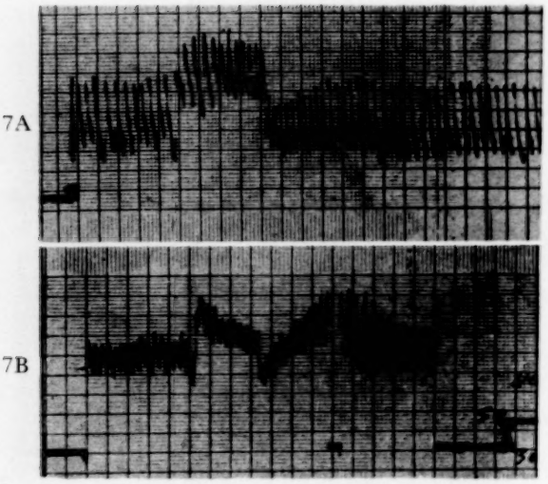


FIG. 7. Effect of positional change on the Valsalva maneuver. Patient E. W. had mitral stenosis; valve area = 1.2 cm.² (30 per cent normal). A, patient in supine position; B, patient in standing position. Note that systemic arterial pressure remained unchanged during a Valsalva maneuver performed in the horizontal position, but decreased rapidly when performed in the standing position.

curve of ventricular function—ventricular stroke work plotted against filling pressure—may assume different slopes depending on altered metabolism and hemodynamics. A similar analysis of ventricular function may be applied to the Valsalva maneuver. The pulmonary capillary wedge pressure is considered to be representative of the left atrial pressure[25,26] and systemic arterial mean and pulse pressures as approximate indexes of the components of left ventricular pressure work, since pulse pressure is roughly proportional to the stroke volume in the same patient. A similar analysis may be made of the function of the right ventricle as well, utilizing right atrial mean pressure and pulmonary arterial mean and pulse pressures.

In the normal patient pulmonary wedge, brachial arterial mean and pulse pressures all fall. (Fig. 2.) A decrease in filling pressure is dependent on an initially normal atrial and pulmonary blood volume which decreases in relation to a momentarily decreased inflow from the right ventricle. This is shown in Figure 2 which depicts the falling pulmonary arterial systolic and mean pressures (decreased right ventricular stroke work) and in Table II which shows the delayed intrathoracic to tongue circulation times. Effective right atrial pressure during straining usually began at zero or soon approximated zero mm. Hg effective pressure and was often lower than the prestraining atrial pressure. Similar low net pressures were recorded in normal subjects by Lee et al.[12] Presumably this lowered effective pressure represented slowing of venous inflow into the great thoracic veins and right heart. (Table II.) Whether or not

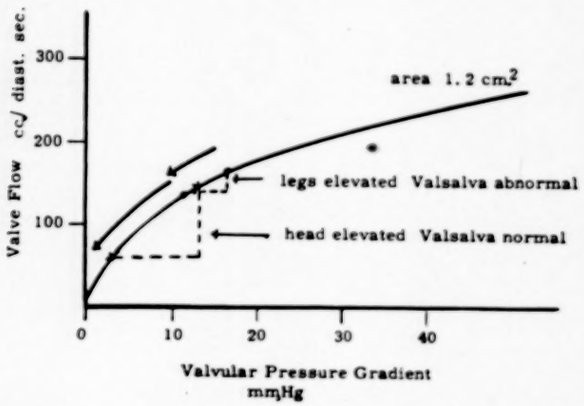


FIG. 8. Effect of changes in position on mitral valvular pressure-flow relations and the resulting Valsalva response. The mitral valve area in patient E. W. was estimated surgically and calculated hydraulically to be 1.2 cm.² The pressure-flow curve for this area is drawn above. For purposes of demonstration, left ventricular diastolic pressure is assumed to be unchanged at 5 mm. Hg during the Valsalva maneuver. Effective pulmonary wedge pressure was measured during straining in two different positions. The valve gradient (PC-5) decreased from 15 to 11 when the legs were elevated 30° and from 12 to 3 when the head was elevated 30°. Note how the changing slope of the pressure-flow curve results in a lesser fall in rate of blood flow through the valve when the legs were up than when the head was up. The arterial blood pressure response was abnormal with a minimally decreased valvular flow and normal when flow decreased more rapidly.

there was tamponade of veins and/or heart,[27] the effective right ventricular filling pressure was decreased and this probably resulted in the decreased pulmonary arterial pressure and flow.

In phase II as systemic vasoconstriction develops[7,12] left ventricular filling pressure may rise with an increase in arterial mean pressure (and presumably stroke work). This succession of events is most probably enhanced by venoconstriction[28] with a rise in peripheral venous pressure followed by a secondary rise in right atrial and pulmonary arterial pressures. (Fig. 2.) The large increases in systemic arterial diastolic pressure seen even in patients with severe aortic insufficiency during phase II would suggest that a part of their low diastolic pressure was related to peripheral vasodilatation.[29]

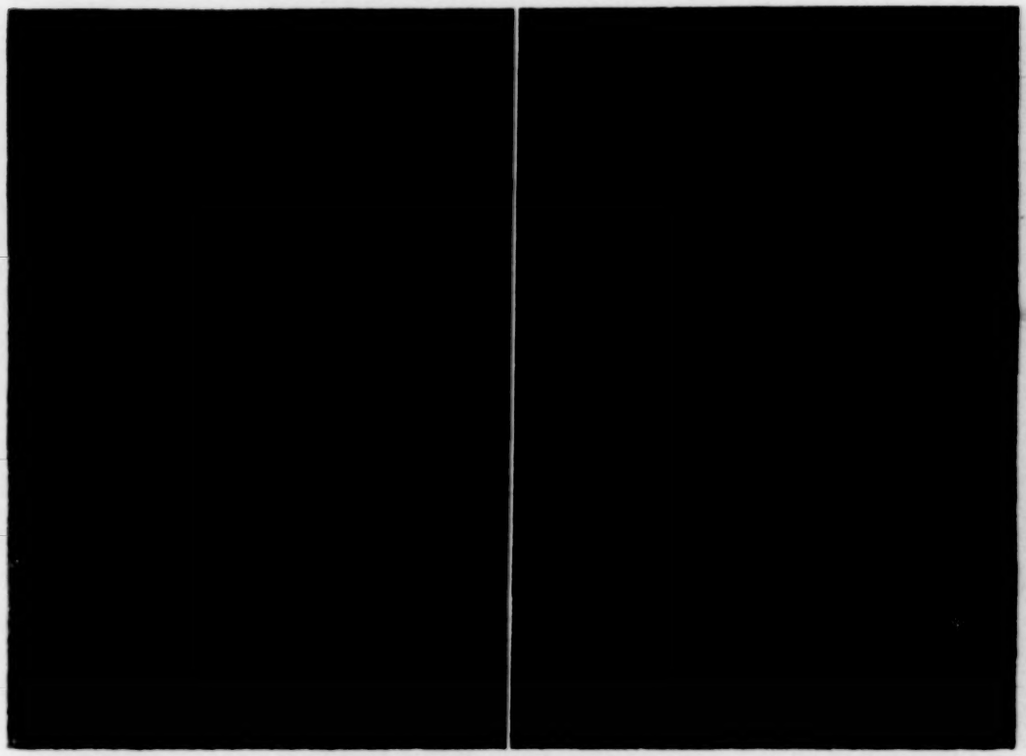


FIG. 9. Effects of commissurotomy and of pregnancy on the Valsalva maneuver in mitral stenosis. Note the change to normal in blood pressure response following mitral commissurotomy in patient H. W. and postpartum in patient N. R. The change in response in patient H. W. is attributed to a larger valve area and lower valve gradient postoperatively. The change in patient N. R. is attributed to a decrease in cardiac output and valve pressure gradient in the postpartum state.

The Abnormal and Intermediate Response. We believe that the difference between the normal and the abnormal response can best be explained in terms of the Starling curve of ventricular function. Sarnoff, Berglund and Case[23,24] have shown in normal dogs that in the high ranges of filling pressure small decreases in pressure do not materially affect stroke work and output. They also demonstrated that constriction of the coronary artery, increased peripheral resistance, anemia and a host of other factors can alter the slope of the work filling pressure curve in a given animal. In similar fashion certain types of heart disease in man can result in a flat ventricular function curve.

Left-Sided Cardiodynamics. An abnormal or intermediate response was seen with left ventricular failure, regardless of the cause, and with tight aortic stenosis. In contradistinction to the normal, arterial pressure (and presumably left ventricular stroke work) remained unchanged while effective pulmonary capillary pressure ("left ventricular diastolic" pressure) slowly decreased during airway straining. This suggested that the left ventricle was on the flat portion of its function curve (Fig. 11) where a fall in filling pressure does not cause stroke work to decrease. In the intermediate group the change in arterial pressure response from abnormal to normal upon tilting the head up was thought to be related to the more sloping ventricular function curve (Fig. 11) of mild left ventricular failure. Tilting is known to cause a decrease in effective filling pressure.[30] If the new level of filling pressure lay on the lower steeper part of the curve, then stroke work and arterial pressure decreased during straining.

The slope of the ventricular function curve, a resultant of the severity of the heart disease, and the accompanying increase in pulmonary blood volume and pressure, which fixed the point on the curve, seemed to be the critical factors. (Fig. 11.) Unchanged arterial pressure during straining, as long as it persisted, probably signified that either the ventricle was working on a flat portion of its function curve or that its filling pressure had not changed. Under most circumstances the flat portion of the curve was associated with elevated

FIG. 10. Effects of pericardiectomy on the responses to the Valsalva maneuver, on venous pressure and circulation time in constrictive pericarditis. Note the final conversion to normal in blood pressure response and its association with a return to normal in venous and pulmonary wedge pressure. A, preoperative tracing: circulation time 22; venous pressure 18. B, one week postoperatively: circulation time 15; venous pressure 18. C, six weeks postoperatively: circulation time 15; venous pressure 7.

filling pressures and therefore left atrial and pulmonary venous congestion.* That an increased atriopulmonary reservoir of blood *per se*[10] is not the primary factor in causing the abnormal pressure response was suggested by the data obtained from patient C. C. She had mitral insufficiency with a large left atrium demonstrated by angiocardiography. The patient was not in failure, however, with a resting pulmonary capillary pressure of 8 mm. Hg. During the Valsalva maneuver, both arterial and pulmonary capillary pressures decreased normally, despite an apparently large reservoir of blood.

Even in the absence of ventricular failure, valvular stenosis itself may cause an abnormal response. Just as the ventricular function curve aids in explaining the abnormal response in myocardial failure the key to understanding mitral stenosis lies in the valvular pressure-flow curve.[31] (Fig. 11.) When the valve area is reduced to 20 per cent of normal, the relationship of pressure to flow across the valve becomes extremely flat. Increasing or decreasing the pressure gradient 5 to 10 mm. of mercury at high levels of pressure results in virtually no change in blood flow across the valve or in left ventricular diastolic volume and pressure.[31] Consequently, stroke work and therefore arterial mean and pulse pressure are unchanged during the period of straining. When the stenosis is less severe, the pressure flow curve is steeper and valve flow is affected more by pressure gradient changes. As demonstrated in patient E. W. with a known valve area of 1.2 cm.^{2} the change in body position from supine to head-up resulted in a decreased mitral valve pressure gradient, a calculated decrease in valvular flow rate and a change in arterial response from abnormal to normal. Valvular pressure-flow relations were changed by surgery in patient L. K. Postoperatively, with a steeper pressure flow curve the Valsalva response became normal.

Judson and co-workers[13] stated that the abnormal Valsalva response was due solely to impaired right ventricular function and to minimizing the "venous blockage effect." Our studies indicate that the abnormal response may result from altered dynamics on either side of the circulation. Seven of the twenty-three patients who had abnormal responses and all but one of the patients with left-sided heart disease who had intermediate responses showed no apparent impairment of right ventricular function. The evidence for this was normal systemic venous or right atrial pressure, delayed intrathoracic circulation time, decrease in pulmonary arterial pulse pressure and low effective right atrial pressure during the straining phase despite an abnormal peripheral arterial response during the Valsalva maneuver.

Right-Sided Cardiodynamics. The abnormal responses which we found in patients with bilateral congestive failure or isolated right ventricular failure are similar to those reported by Judson and co-workers. Unchanged intrathoracic circulation times (Table II) and pulmonary arterial pulse pressures (Fig. 5) during the maneuver indicated that left atrial pressures were kept at elevated and minimally decreasing levels by essentially unchanged right ventricular work and output. In four of six studies on circulation time, blood flow into the chest was impeded while blood flow out of the right heart was not. This may have been due to precardiac

* Bondurant and Hickam have shown that acute pulmonary engorgement induced by G-suit inflation even in the normal person is associated with an intermediate Valsalva response.[36]

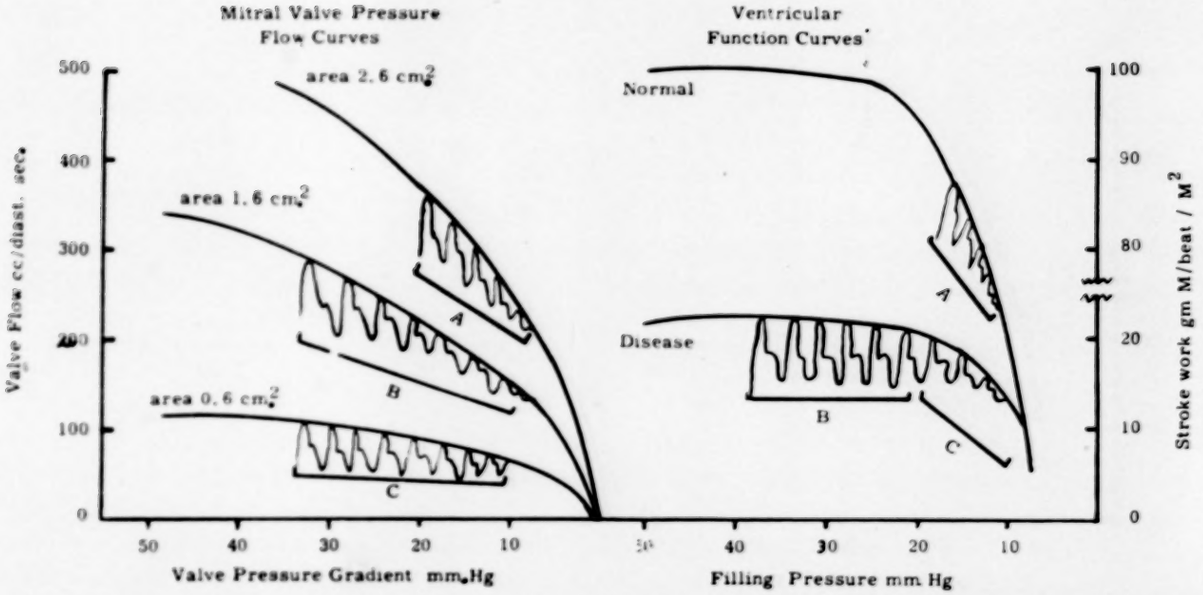


FIG. 11. Relation of arterial pressure response to valvular hydraulics and to ventricular function. Ventricular function (Starling) curves are patterned after Sarnoff, Berglund and Case,[23,24] but are drawn backwards to match the direction of change in blood pressure during straining. The points A and C demonstrate how the slope of the curve affects the response; point B shows that when filling pressure is high enough to lie on the flat part of the curve, an abnormal response results. The slope of the valvular pressure-flow curve[31] affects valvular flow and the type of arterial pressure response in similar fashion to the ventricular function curve. Pulmonary congestion places the starting point of the phenomenon further to the left toward the flatter part of the pressure-flow curve.

tamponade in association with a flat (failure-type) right ventricular function curve. The other two patients could not exceed 25 to 30 mm. Hg airway pressure; neither thoracic venous inflow nor right heart outflow were impeded. Whether this was related to less effective tamponade or to a greater splanchnic venous reservoir cannot be stated. The unchanged pulmonary arterial flow and pressure in these patients suggest that there is little significant increase in pulmonary vascular resistance during airway straining such as is seen in the open-chest dog.[32]

No observations were made in this study of the effect of severe pulmonic stenosis or tricuspid stenosis.

The role of systemic vasoconstriction as the sole cause of the abnormal response is excluded by Greene and Bunnell's observations[10] that with tetraethylammonium chloride therapy sufficient to abolish the phase IV vasoconstrictor overshoot the abnormal response of phase I remained unchanged in patients with mitral stenosis. That severe acute vasoconstriction with norepinephrine can change a normal blood pressure response to an intermediate type was shown by Price and Connor.[11] They believed this was related to acute pulmonary plethora[33] and by inference to an acute change in left ventricular function as well.[23,24]

Circulation During the Overshoot. The hypertension of the overshoot phase normally is due to the combination of vasoconstriction plus acceleration of blood flow out of the chest.[2,7] Occasionally, a small overshoot was seen in a patient with an intermediate response. Two possible explanations for this are (1) the final falling off of pressure in phase II may have been sufficient stimulus for further vasoconstriction and (2) because the overshoot rise in arterial pressure was no greater than the overshoot rise in pulmonary wedge pressure, no change took place in net left ventricular work.

A difference in the time of arrival was noted between the overshoot peaks in the pulmonary capillary and systemic arterial pressures in patients with mitral stenosis. The wedge pressure overshoot occurred alone or preceded any brachial arterial overshoot by about four seconds. Normally and in mitral insufficiency, for example, the overshoots in pulmonary capillary and arterial pressures peak simultaneously. Presumably the delayed or absent overshoot in the arterial pressure[6] was related to a delayed build-

up of left ventricular diastolic volume and pressure due to the mitral stenosis and its peculiar pressure-flow relations. Whether this delay may be helpful as an aid in separating valvular obstruction from left ventricular failure is presently under investigation.

CLINICAL APPLICATIONS

An abnormal test is the result of left ventricular failure, right ventricular failure, or tight mitral or aortic stenosis. The finding of an abnormal response may be attributed to a left-sided cardiac lesion only when right ventricular failure is absent. The test is used to best advantage in the study of borderline rather than overt cases. This may be done at the bedside utilizing an ordinary sphygmomanometer.[8] The type of response can be detected accurately in 80 per cent of patients. Moderate degrees of left ventricular failure give an abnormal response. Thus in the differential diagnosis of dyspnea, particularly in the elderly arteriosclerotic patient with emphysema, this maneuver can quickly disclose a cardiac component.

Tight aortic stenosis results in an abnormal response. The early clinical and even laboratory diagnosis of dynamically significant aortic stenosis is at best difficult.[34] A flat ventricular function curve is characteristic of a tight valve. The Valsalva maneuver demonstrated this important physiologic abnormality quickly and easily.

Tight mitral stenosis similarly results in an abnormal response. No patient with an abnormal or intermediate response had a measured or calculated valve area greater than 1.6 cm.^{2} Those patients with a mitral murmur and a normal response had little or no disability and only minor evidence of physiologic abnormality by other tests.

The clinical use of the Valsalva maneuver is not so important in lesions of the right side of the heart which are accessible to other forms of bedside study.

Changes in the test are indicative of the measure of success of therapy such as digitalization and diuresis. Patients with mitral disease have been followed up during pregnancy using the abnormal response as evidence of severe pulmonary congestion. Similarly, patients with myocardial infarction, in whom there is a question of associated congestive failure, could be simply and easily tested. This was shown in patients A. B. and J. P. who went into clinical shock following myocardial infarction. At this time the Valsalva response was abnormal. Both were thought to have acute myocardial failure; each was digitalized with clinical improvement and conversion of the response to normal. Likewise, changes in the response during administration of large amounts of intravenous fluids may give early warning of impending pulmonary edema in elderly patients and patients with cardiac disease.[13]

Nineteen of twenty-three patients with an abnormal response to the Valsalva maneuver were class III or IV cardiac patients. Other tests of circulatory function were frequently abnormal and no patient in this group failed to have either an elevated pulmonary wedge or systemic venous pressure.

Patients with an intermediate response usually were class II cardiac patients. They had evidence of heart disease but without marked alterations in other tests of circulatory function except for pulmonary capillary pressure. Systemic venous pressures were normal in all but the one patient with cor pulmonale.

The patients with a normal response had little or no evidence of markedly altered ventricular function or valvular hydraulics. Evidence of decreasing left ventricular stroke work (a normal response) indicated that these curves and the functions they represented were normal or nearly so. (Fig. 11.) The only exception might have been when ventricular filling pressures were so low that they lay on the sloping part of even an abnormal curve. (Fig. 11.) This may have occurred in patient H. C. with atrial septal defect, severe pulmonary hypertension and a small right-to-left shunt. The common atrial pressure was 3 mm. Hg and this decreased even further during straining. The Valsalva response was borderline normal but with no overshoot.

The test should be done in the supine position. An abnormal response should be followed by repetition in the head-up position on a tilt table and a normal response by repetition in the elevated leg position. The final result can be classified as normal, intermediate or abnormal.

The advantages of the test are simplicity, rapidity, reliability and sensitivity to change. On the other hand, the test requires the patient's complete cooperation, and errors occur if the maneuver is improperly performed. If the airway pressure is inaccurately or slowly elevated to a maximum or if the test is begun from the extreme expiratory mid-position, a false positive response may result. If airway pressure is per-

mitted to fall once the peak has been obtained, then a falsely normal test results.

The only potential hazard of the Valsalva maneuver is hypotension and low coronary perfusion pressure in patients with a normal response. In a single individual with severe coronary disease, an attack of angina pectoris resulted after seven successive prolonged maneuvers. The attack cleared quickly with nitroglycerine. Such episodes have since been avoided by restricting the period of straining to ten seconds and not repeating the test unnecessarily in susceptible patients. Because coronary perfusion can be decreased markedly in phase II the electrocardiographic changes during straining are presently under study.[35]

SUMMARY

Eighty-eight observations were made in seventy-eight subjects: seven normal persons and seventy-one patients with various forms of heart and lung disease. Directly recorded and ausculted arterial pressure measurements were obtained during the Valsalva maneuver. Other tests of circulatory and pulmonary function were performed as indicated, including cardiac catheterization in forty-two subjects. The clinical and physiologic results were correlated.

A normal arterial pressure response during forced expiration (falling arterial pressure) was observed in normal subjects, in pregnancy and in heart disease without heart failure or vascular stenosis.

An abnormal arterial pressure response (unchanged arterial pressure) was observed in twenty-three patients with left or right ventricular failure or tight aortic or mitral stenosis (0.5 to 1.0 cm.^{2}). Most patients in this group were in class III or IV. There was good correlation with abnormalities in other tests of cardiac function including elevated pulmonary capillary wedge and/or right atrial pressures.

Twenty-six patients showed an intermediate response; in these an abnormal test either could be elicited by alterations in body position or was inconstant in degree and frequency. These cardiac patients were usually in class II, with either mild left ventricular failure or mild to moderately severe mitral stenosis (0.8 to 1.5 cm.^{2}) or tight aortic stenosis; there was one patient with chronic cor pulmonale. Correlations with tests of cardiac function other than elevated pulmonary wedge pressure were not striking.

The difference between the normal and the abnormal Valsalva response was believed to depend on a flattened ventricular function curve or a flattened valvular pressure-flow curve. The simplicity and reliability of the Valsalva maneuver as a clinical test utilizing an ordinary blood pressure cuff is emphasized. Its greatest clinical value lay in the fact that, in the absence of severe right ventricular failure, the test can detect early left ventricular failure, tight mitral stenosis or tight aortic stenosis.

Acknowledgment: The authors are grateful to Doctors D. Pitcairn and C. S. Burwell for the data on patient A. S., to Hospital Corpsmen Herbert P. Fletcher, Sandy J. Smith, Robert W. Guinee, George D. Bates and Morris H. Smith for their invaluable technical assistance throughout this study, and to Doctors R. B. Case, J. L. Patterson and D. Richardson for their helpful comments.

REFERENCES

1. Derbes, V. J. and Kerr, A., Jr. Valsalva's maneuver and Weber's experiment. *New England J. Med.*, 253: 822, 1955.
2. Flack, M. Some simple tests of physical efficiency. *Lancet*, 1: 210–212, 1919.
3. Rushmer, R. F. Circulatory effects of three modifications of the Valsalva experiment. *Am. Heart J.*, 34: 399, 1947.
4. Wilkins, R. W., Culbertson, J W. and Smithwick, R. H. The effects of various types of sympathectomy upon vasopressor responses in hypertensive patients. *Surg., Gynec. & Obst.*, 87: 661, 1948.
5. Sarnoff, S. J., Hardenburgh, E. and Whittenberger, J. L. Mechanism of the arterial pressure response to the Valsalva test. *Am. J. Physiol.*, 154: 316, 1948.
6. Goldberg, H., Elisberg, E. I. and Katz, L. N. The effects of the Valsalva-like maneuver upon the circulation in normal individuals and patients with mitral stenosis. *Circulation*, 5: 38, 1952.
7. Sharpey-Schafer, E. P The peripheral circulation in circulatory failure. *Brit. M. Bull.*, 8: 331, 1952.
8. Knowles, J. H., Gorlin, R. and Storey, C. F. Clinical test for pulmonary congestion with use of the Valsalva maneuver, *J. A. M. A.*, 160: 44, 1956.
9. Hamilton, W. F., Woodbury, R. A. and Harper, H. T. Arterial, cerebrospinal and venous pressures in man during cough and strain. *Am. J. Physiol.*, 141: 42, 1944.
10. Greene, D. G. and Bunnell, I. L. The circulatory response to the Valsalva maneuver of patients with mitral stenosis with and without autonomic blockade. *Circulation*, 8: 264, 1953.
11. Price, H. L. and Conner, E. H. Certain aspects of the hemodynamic response to the Valsalva maneuver. *J. Appl. Physiol.*, 5: 449, 1953
12. Lee, G. deJ., Matthews, M. B. and Sharpey-Schafer, E. P. The effect of the Valsalva maneuver on the systemic and pulmonary arterial pressures in man. *Brit. Heart J.*, 16: 311, 1954

13. Judson, W. E., Hatcher, J. D. and Wilkins, R. W. Blood pressure responses to the Valsalva maneuver in cardiac patients with and without congestive failure. *Circulation*, 11: 889, 1955.
14. Stucki, P., Hatcher, J. D., Judson, W. E. and Wilkins, R. W. Studies of circulation time during the Valsalva test in normal subjects and in patients with congestive failure. *Circulation*, 11: 900, 1955.
15. Sharpey-Schafer, E. P. Effects of Valsalva's maneuver on the normal and failing circulation. *Brit. M. J.*, 1: 693, 1955.
16. Criteria for Classification and Diagnosis of Heart Disease, New York Tuberculosis and Health Association, 3rd ed., 1932.
17. Hellems, H. K., Haynes, F. W. and Dexter, L. Pulmonary "capillary" pressure in man. *J. Appl. Physiol.*, 2: 24, 1949.
18. Unpublished observations.
19. Bjurstedt, H. Influence of the abdominal muscle tone on the circulatory response to positive pressure breathing in anesthetized dogs. *Acta physiol. Scandinav.*, 29: 145–162, 1953.
20. Otis, A. B., Rahn, H. and Fenn, W. O. Venous pressure changes associated with positive intrapulmonary pressures; their relationship to the distensibility of the lung. *Am. J. Physiol.*, 146: 307, 1946.
21. Burwell, C. S. The management of heart disease in pregnant women. *Bull. Johns Hopkins Hosp.*, 95: 130, 1954.
22. Gorlin, R., Lewis, B. M., Haynes, F. W., Spiegl, R. J. and Dexter, L. Factors regulating pulmonary "capillary" pressure in mitral stenosis. *Am. Heart J.*, 41: 834, 1951.
23. Sarnoff, S. J. and Berglund, E. Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. *Circulation*, 9: 706, 1954.
24. Case, R. B., Berglund, E. and Sarnoff, S. J. Ventricular function. II. Quantitative relationship between coronary flow and ventricular function with observations on unilateral failure. *Circulation Res.*, 2: 319, 1954.
25. Dow, J. W. and Gorlin, R. Pulmonary "capillary" pressure as an index of left atrial mean pressure in dogs. *Federation Proc.*, 9: 33, 1950.
26. Epps, R. G. and Adler, R. Left atrial and pulmonary capillary venous pressure in mitral stenosis. *Brit. Heart J.*, 15: 298, 1953.
27. Sarnoff, S. J. Personal communication.
28. Page, E. B., Hickam, J. B., Sieker, H. O., McIntosh, H. D. and Pryor, W. W. Reflex venomotor activity in normal persons and in patients with postural hypotension. *Circulation*, 11: 262, 1955.
29. Lewis, T. Studies of capillary pulsation with special reference to vasodilatation in aortic regurgitation and including observations on the effects of heating the human skin. *Heart*, 11: 151, 1924.
30. Brigden, W. and Sharpey-Schafer, E. P. Postural changes in peripheral blood flow in cases with left heart failure. *Clin. Sc.*, 9: 93, 1950.
31. Gorlin, R. and Gorlin, S. G. Hydraulic formula for calculation of the area of the stenotic mitral valves, other cardiac valves and central circulatory shunts. *Am. Heart J.*, 41: 1, 1951.
32. Brecher, G. A. and Hubay, C. A. Dynamic aspects of pulmonary artery flow with controlled respiration. *Federation Proc.*, 14: 17, 1955.
33. Sarnoff, S. J., Berglund, E. and Sarnoff, L. C. Neurohemodynamics of pulmonary edema. III. Estimated changes in pulmonary blood volume accompanying systemic vasoconstriction and vasodilation. *J. Appl. Physiol.*, 5: 367, 1953.
34. Gorlin, R., McMillan, I. K. R., Medd, W. E., Matthews, M. B. and Daley, R. Dynamics of the circulation in aortic valvular disease. *Am. J. Med.*, 18: 855, 1955.
35. Case, R. B. and Gorlin, R. Unpublished observations.
36. Bondurant, S. and Hickam, J. B. Personal communication.

Coronary Arteriovenous Fistula*

Clinical and Physiologic Report on Two Patients, with Review of the Literature

RAYMOND J. WALTHER, M.D., GEORGE W. B. STARKEY, M.D., EVANGELINE ZERVOPOLUS, M.D. *and* GLEN A. GIBBONS, M.D.†

Boston, Massachusetts

PATENT ductus arteriosus is the most common cause of a continuous precordial murmur. Another cause of the continuous murmur is a fistulous communication between the coronary artery and the right heart. This abnormality when occurring as an isolated lesion may produce findings closely resembling or perhaps indistinguishable from the patent ductus. Recently we have observed two patients with coronary arteriovenous fistulas, both of whom have been studied by venous catheterization. In this report the clinical features of this anomaly and its effect on the circulation will be presented along with a review of the literature.

MATERIALS AND METHODS

The two patients reported herein were seen in the outpatient department of the Pediatric Service at the Boston City Hospital. Venous catheterization was performed in the conventional manner with the patients in the resting state. Pressures were recorded by a Sanborn electromanometer and a Statham strain gage with the zero point of reference as the skin of the back. Cardiac outputs were determined according to the Fick principle.

CASE REPORTS

CASE I. E. L., an eight year old white girl was found to have a heart murmur three months after birth. She had developed normally and was in every way able to keep up with her contemporaries. There were no symptoms referable to the cardiovascular system.

On physical examination the blood pressure was 130/84. The patient was well developed and nourished. No cardiac enlargement was present. There was a grade V roaring continuous murmur accompanied by a thrill, maximal in the fourth and fifth intercostal spaces close to the left sternal border. Just medial to the apex and in the pulmonic area the murmur was more to and fro rather than continuous in timing. The pulmonic closure was normal in intensity and normally split. There was no cyanosis or clubbing and no evidence of peripheral congestion.

The electrocardiogram showed no abnormalities. X-ray and fluoroscopy of the chest revealed a slightly enlarged left atrium, and slight increase in the pulmonary vascular markings. (Fig. 1.) The phonocardiogram demonstrated crescendo-decrescendo murmurs in systole and diastole. (Fig. 2.)

Hemodynamic data are seen in Table I. The catheter entered the coronary venous system. Blood drawn from the distal coronary sinus contained the usual small amount of oxygen, but blood drawn from the middle cardiac vein was fully saturated with oxygen. The position of the catheter in the middle cardiac vein is seen in Figure 3. The calculated shunt of oxygenated blood into the right side of the heart was 5.2 L./minute.

CASE II. P. S., a fourteen year old white girl was first known to have a cardiac murmur at the age of twelve months. There were never any symptoms referable to the cardiovascular system and development had been normal.

On physical examination, the blood pressure was 120/70. The patient was well developed and obese. No abnormal venous or arterial pulsations were present. The apical impulse was forceful and was located 1 cm. lateral to the mid-clavicular line in the fifth intercostal space. A grade II continuous machinery murmur was heard at the left sternal border, maximal in the second intercostal space. The pulmonic closure was normal in intensity and normally split. There was no cyanosis, clubbing or evidence of peripheral congestion.

* From the Circulation Laboratory of the Tufts University Medical Service, the Boston University Pediatric, and the Thoracic Surgical Services of the Boston City Hospital, Boston, Massachusetts. Supported in part by grants from the National Heart Institute, United States Public Health Service, and the Massachusetts Heart Association.

† Present address: San Diego, California.

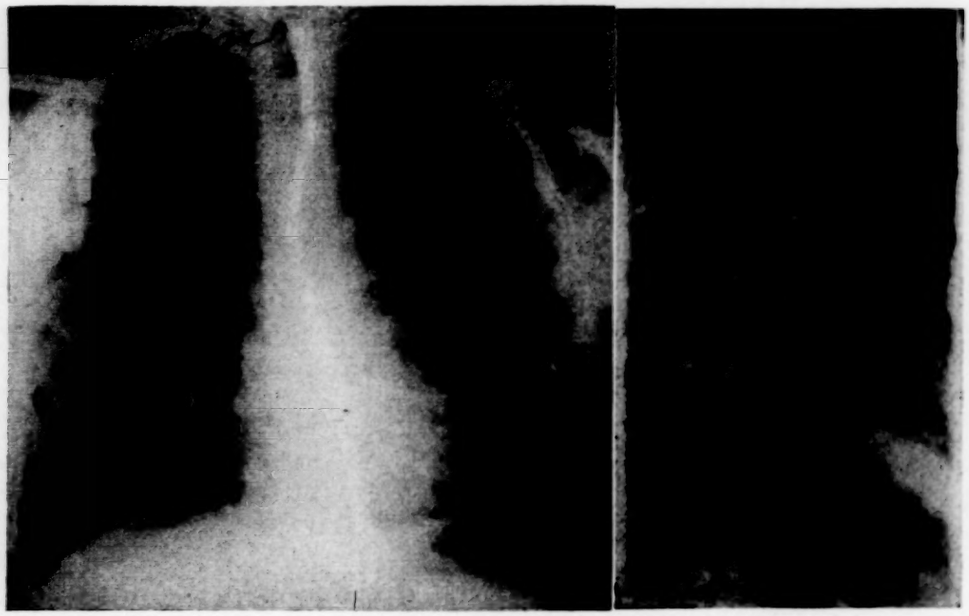


FIG. 1. Case I. Posteroanterior and right anterior oblique films demonstrating slight prominence of the pulmonary vascular markings and slight enlargement of the left atrium.

X-rays and fluoroscopy of the chest revealed slightly increased transverse diameter of the heart and prominence of the main pulmonary artery. (Fig. 4.) The heart and lung fields were otherwise within normal limits. The electrocardiogram disclosed a frontal axis of 0° and ST, T wave abnormalities in standard lead I and AVL. (Fig. 5.) A phonocardiogram demonstrated the continuous murmur. (Fig. 6.)

The clinical picture strongly favored patent ductus arteriosus, but at thoracotomy this diagnosis was not confirmed. A continuous thrill was felt over the main pulmonary artery, this structure being moderately enlarged. The thrill could be abolished by briefly occluding the pulmonary artery at the valve. Obstruction just distal to this point failed to eliminate the thrill. Careful dissection of the pulmonary artery and aorta to their bases revealed no fenestrum. On examination of the anterior surface of the right ventricle, a continuous thrill was felt over the right coronary artery. When the heart was rotated out of the pericardium an aneurysm-like dilatation of the right coronary artery became visible about 3.0 cm. from the pulmonary valve. The vessel projected above the surface of the myocardium, but was deeply imbedded in its substance. There was a deep groove as this vessel crossed the upper part of the right ventricle and it seemed to disappear into the right ventricular myocardium just proximal to the pulmonic valve. The thrill could not be completely abolished by compression of the dilated portion of the right coronary artery. No attempt was made to ligate the abnormal vessel. The conclusion at surgery was that a communication was present between the right coronary artery and the outflow tract of the right ventricle or the pulmonary artery. Figure 7 is a sketch of the findings at operation.

Venous catheterization was performed on September 22, 1955. (Table II.) The results were consistent with the anatomic situation observed at operation. The pulmonary artery blood contained from 14 to 26 cc./L. more oxygen than the right ventricular blood. The evidence favors a communication distal to the pulmonic valve.

COMMENTS

General Considerations. Eleven case reports of coronary arteriovenous fistulas occurring as the only congenital lesion have been collected from the literature and are listed in Table III, Cases 1 to 11. Of these, four anatomic variants have been described. Arterial blood from the coronary tree may drain into the right atrium directly or by way of the coronary sinus, or into the right ventricular outflow tract or into the pulmonary artery. The consequent left to right shunt adds to the volume work of the left ventricle because this chamber must handle not only the peripheral flow but the portion which runs off into the central venous system. If the receiving chamber is the right atrium or ventricle, then the right ventricle also participates in the increased volume work; but if drainage is into the pulmonary artery, the additional volume load is handled by the left ventricle alone. In any case, the shunted blood must traverse the pulmo-

nary circuit and its flow is consequently greater than systemic tissue flow.

Clinical Features. Murmur: Since there is a pressure gradient from the arterial to the venous system in systole and diastole, shunting is present throughout the cardiac cycle and the murmur is

TABLE I
HEMODYNAMIC DATA IN CASE I*

A

Site	Pressures (mm. Hg)			Blood O_2 Content (cc. per L.)
	Systolic	Diastolic	Mean	
Superior vena cava	...	..	..	124
Inferior vena cava	...	..	..	118
Right atrium	...	..	4	125
Middle cardiac vein (occluding)	31	4	..	159 (101% sat.)
Right ventricle	30	6	..	144
Main pulmonary artery	30	13	21	143
Right pulmonary artery	27	11	19	139
Right "pulmonary capillary"	...	..	9	.....
Distal coronary sinus	45	12	..	62
Femoral artery	130	84	..	165 (99% sat.)

B

	Blood Flows	
	L. per min.	L. per M^2 per min.
Pulmonary	11.1	11.7
Peripheral	5.9	6.2
Left to right shunt	5.2	5.5

Note: Zero point of reference, skin of the back.
* Patient E. L., chest diameter 13.5 cm., body surface area 0.95 M^2.

likely to be continuous. In eight of the reported ten cases in which the auscultatory findings were described, a continuous murmur was heard. However Halpert's [*1*] patient exhibited only a systolic murmur, and Colbeck and Shaw [*8*] described aortic systolic and diastolic murmurs in one case. The murmur in one of our patients, E. L., sounded continuous at the apex, but to and fro at the fourth left intercostal space. Our second patient, P. S., had a continuous murmur. Of the patients exhibiting a murmur in both systole and diastole, the site of maximum intensity was to the left of the sternum in all but one. In six patients the murmur was best heard in the pulmonic area, and in three it was also easily audible an interspace or more below. The mid and lower left sternal border was the site of maximum intensity in two patients and the lower right sternal border in one. The location was not described in another. Characteristically, the murmur of a patent ductus is heard best in the second intercostal space just lateral to the pulmonic area [*12*]. It is usually heard well up to the clavicle and is transmitted to the axilla and

TABLE II
HEMODYNAMIC DATA IN CASE II*

A

Site	Pressures (mm. Hg)			Blood O_2 Content (cc. per L.)
	Systolic	Diastolic	Mean	
Superior vena cava	...	..	..	118
Right atrium	...	..	11	114
Right ventricle	27	7	..	115
Pulmonary artery (at valve)	32	15	25	129
Pulmonary artery (distal)	33	17	25	141
Left pulmonary artery	...	..	..	132
Middle cardiac vein	36	4	..	51
Left brachial artery	102	65	75	177 (98% sat.)

B

	Blood Flows	
	L. per min.	L. per M^2 per min.
Pulmonary	7.0	4.1
Peripheral	5.0	2.9
Left to right shunt	2.0	1.2

Note: Zero point of reference, skin of the back.
* Patient P. S., chest diameter 23.5 cm., body surface area1.72 M^2.

posteriorly to the right of the scapula. Because of location of the murmur in the pulmonic area, the diagnosis of patent ductus arteriosus might easily have been made in at least six of these patients. On the other hand, the presence of a continuous murmur heard best in a site not typical for the ductus should arouse suspicion that this is not the anomaly present. Since the auscultatory findings in all lesions associated with a continuous precordial murmur may bear striking resemblances, it is pertinent to outline the other causes here: (1) Acquired or congenital aneurysm of the sinus of Valsalva with communication between it and the right atrium or ventricle may cause a continuous murmur. Its maximum intensity is usually lower in location than that of a patent ductus [*13*]. (2) An aortic pulmonary septal defect by auscultation may closely resemble the findings of patent ductus,

TABLE III

CLINICAL DATA ON THIRTEEN PATIENTS WITH CORONARY ARTERIOVENOUS FISTULA

Case	Report	Age and Sex	Age Murmur First Heard	Murmur	Thrill	Blood Pressure	X-Ray and or Fluoroscopy	Electrocardiogram	Pathologic Anatomy	Comment
1.	Halpert [*1*], 1930	54,* M.	.....	Apical systolic	No	125/70	Normal	.....	Right coronary artery to right atrium;† heart weight 500 gm.	No cardiac symptoms; died of carcinoma of stomach
2.	Löwenheim [*2*], 1932	62,* F	.....	.....	....	260/100	.....	.....	Right coronary artery to right atrium;† heart weight 835 gm.; both ventricles hypertrophied	.....
3.	Harris [*3*], 1937	43,* M	.....	.....	....	.....	.....	.....	Right coronary artery to right atrium†	No cardiac symptoms; died of intracranial tumor
4.	Biörck and Crafoord [*4*], 1947	10, M	7 yr.	Machinery murmur in pulmonic area	No	135/80	Left heart border rounded, prominence of pulmonary artery; hilar dance	Normal	Probable left coronary to pulmonary artery†	Two transient episodes of dyspnea; anomalous vessel ligated surgically
5.	Paul et al. [*5*], 1949	9, M	9 yr.	Continuous murmur lower right sternal border	No	110/75	Slight cardiac enlargement	Normal	Right coronary artery to coronary sinus†	No cardiac symptoms; no attempt to close vessel at operation
6.	Brown and Burnett [*6*], 1949	13 mo., M	7 mo.	Continuous murmur heard best along lower left sternal border	Yes	.....	At 7 mo. heart enlarged to left and right, pulmonary artery prominent and left atrium enlarged	Normal	Vessel from posterior aortic sinus to right ventricle;† right atrium dilated and right ventricle hypertrophied	No cardiac symptoms; died of acute laryngotracheobronchitis
7.	Baylis and Campbell [*7*], 1952	76,* F	48 yr.	Continuous murmur 2nd and 3rd left intercostal space	Yes	175/85	Prominence of pulmonary artery and left ventricle	Left axis deviation, left ventricular preponderance	Left coronary artery to pulmonary artery;† both ventricles hypertrophied	Died of carcinoma of breast with lymphangitic spread to lungs causing congestive heart failure
8.	Colbeck and Shaw [*8*], 1954	86,* M	85 yr.	Aortic systolic and diastolic, and mitral systolic	No	170/80	Cardiac enlargement	Left bundle branch block atrial fibrillation	Right coronary artery to right atrium;† left ventricle hypertrophied, right atrium and right venticle dilated	Died of congestive heart failure
9.	Davison et al. [*9*], 1955	58,* M	57 yr.	Systolic and diastolic machinery murmur at pulmonic area	Yes	125/55	Generalized cardiac enlargement, pulmonary congestion	Atrial fibrillation	Left coronary artery to coronary sinus;† hypertrophy of right and left ventricles	Died of congestive heart failure
10.	Sondergaard [*10*], 1955	11, M	.....	Continuous murmur at 2nd left and 4th left intercostal space	Yes	.....	Normal	.....	Left coronary artery to right ventricle*	Dyspnea on exertion; aberrant vessel ligated surgically
11.	Davis et al. [*11*], 1956	19, F	19 yr.	Continuous machinery murmur at pulmonic area	?	110/80	Normal	Normal	Coronary artery to infundibular portion of right ventricle†	No cardiac symptoms; anomalous vessel ligated and divided
12.	Authors' Case I, E. L.	8, F	1 yr.	Grade IV continuous murmur at lower sternal border 4th and 5th intercostal spaces; to and fro murmur medial to apex	No	130/84	Slightly enlarged left atrium and pulmonary artery and increase in pulmonary vascular markings	Normal	Probable coronary artery to middle cardiac vein†	No cardiac symptoms
13.	Authors' Case II, P. S.	13, F	3 mo.	Grade II continuous machinery murmur at upper sternal border in 2nd intercostal space	No	120/70	Slight prominence of main pulmonary artery and slight increase in total diameter of heart	ST, T wave abnormalities of lead 1, AVF	Probable right coronary artery to pulmonary artery	No cardiac symptoms; thoracotomy performed; no corrective procedure done

* Age at time of death.
† Site of arteriovenous fistula.

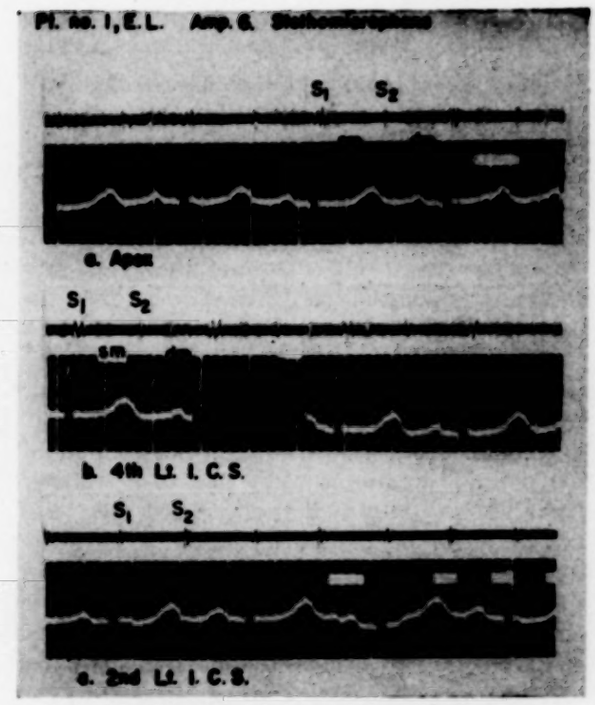


FIG. 2. Case 1. Phonocardiogram demonstrating a continuous murmur at the apex and lower left sternal border. The murmur seems to have its greater intensity in mid-systole and mid-diastole.

although the maximum intensity of the murmur may be lower than the second intercostal space [*14*]. (3) Collateral circulation between the bronchial and pulmonary arteries in truncus and pseudotruncus arteriosus may exhibit a continuous murmur heard usually over the whole thorax [*15,16*]. (4) Total anomalous pulmonary venous drainage into the left innominate vein has been described as a cause of a continuous murmur, usually softer than that of a patent ductus, and best heard in the pulmonic area [*17*]. (5) Pulmonary arteriovenous fistulas may produce a continuous murmur heard over the precordium. Numbers 3 to 5 are most commonly accompanied by visible cyanosis unless a very high pulmonary flow is present, and as a rule are not difficult to distinguish from the acyanotic group.

Electrocardiograms: The increased volume work imposed upon the heart may be borne either by the left ventricle alone, or in most instances by both ventricular chambers. In the first instance, if the load is sufficient, the electrocardiographic pattern of left ventricular hypertrophy would evolve. In the latter case, also if volume work is large enough, a pattern of combined ventricular hypertrophy might be expected. In nine of the reported cases, including our two, electrocardiographic findings were described. In five patients the records were normal. Left axis deviation and left ventricular preponderance were noted in one, left bundle branch block and

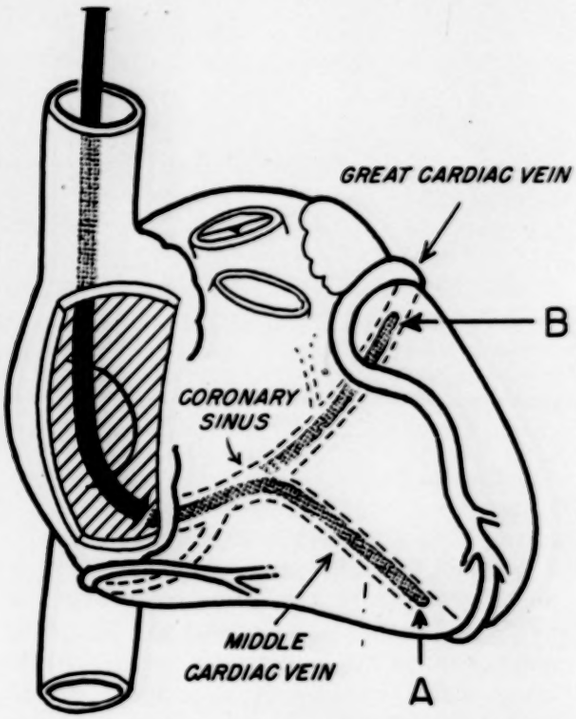


FIG. 3. Case 1. Drawing from films taken during catheterization illustrating the position of the catheter in the middle cardiac vein and the distal coronary sinus. Samples were taken approximately at sites A and B.

atrial fibrillation in one, and ST, T wave abnormalities were present in our second patient, P. S. Atrial fibrillation without other abnormalities were recorded in two patients. It is unlikely that the atrial fibrillation in the two cases was related to the coronary arteriovenous fistula. In one instance the patient was in congestive failure as a result of lymphangitic spread of cancer of the breast to the lungs, and the second patient was eighty-six years of age.

Roentgenographic and fluoroscopic findings: Ventricular enlargement seen on x-ray and fluoroscopy should roughly parallel the electrocardiographic expression of selective chamber overwork as commented on previously. Prominence of the pulmonary artery, increased pulmonary vascular markings, and hilar dance are not uncommon findings in congenital lesions with increased pulmonary blood flow. In nine of the reported cases

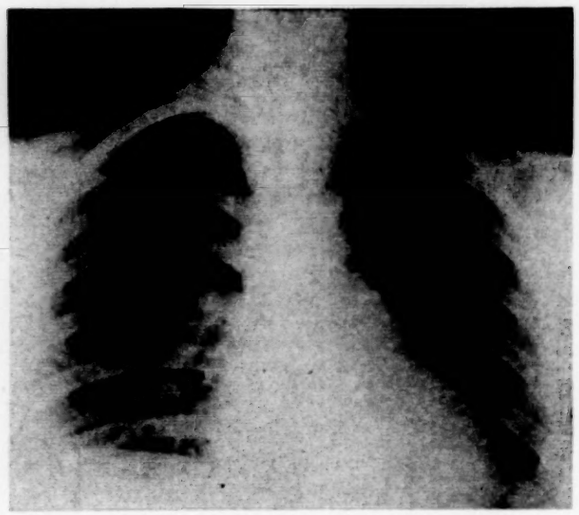


FIG. 4. Case II. Posteroanterior projection showing slight increase in transverse diameter of the heart. Fluoroscopy revealed slight prominence of the main pulmonary artery segment.

radiographic studies were described, and of these six were abnormal. The data, including that on our two cases are shown in Table III. Prominence of the main pulmonary artery appeared in five, cardiac enlargement was reported in four, left ventricular prominence in two, and left atrial enlargement in two. Pulmonary congestion was present in one patient with congestive failure. In Biörck's patient a hilar dance was observed, and in our first patient, E. L., the pulmonary vascular markings were increased. Enlargement of the left atrium, noted in patient E. L. and in the patient presented by Brown and Burnett is similar to that seen in other congenital lesions associated with large left to right shunts, for example, ventricular septal defect or patent ductus arteriosus.

Hemodynamic studies: In two of the cases reported, data obtained from venous catheterization are listed. Flows and pressures are recorded in the case presented by Davison et al. Flows can be computed from the values of blood oxygen content and oxygen consumption given by Davis et al. in their case. The data from these two reports is tabulated with that from our two patients in Table IV.

In the fifty-eight year old patient of Davison, the right atrial, right ventricular and pulmonary arterial pressures were elevated. This subject was clinically decompensated at the time of the study. Although pulmonary vascular resistance cannot be accurately calculated, the elevation of pulmonary arterial pressure suggests that pulmonary vascular resistance is slightly increased. The left to right shunt was 3.9 L./minute. This patient had a rapid downhill course of congestive failure which terminated fatally. The coronary arteriovenous fistula seems to have been a major cause of congestive failure in only this case.

The patient reported by Davis et al. and our second patient, P. S., are nearly comparable in respect to both the anatomic diagnosis and catheterization findings. Pressures in both instances were normal and the flows were almost the same. The left to right shunt was small in both and should be handled by the heart without difficulty.

In our first patient, E. L., the pulmonary blood flow was about twice that of peripheral flow. The pressures were normal and there was no evidence of increased resistance to flow through the lungs. This patient's left to right shunt (5.2 L./minute) was the largest of the group.

Diagnosis: The clinical diagnosis of coronary arteriovenous fistula as is demonstrated in the cases under discussion is difficult. In all patients except one, E. L., the diagnosis was made at the time of operation or by necropsy. The preoperative diagnoses in the six subjects having thoracotomy were: patent ductus in four, aorticopulmonic fistula in one, and arteriovenous fistula, exact site undetermined in one. In patient E. L. the unusual location of the continuous murmur along the lower left sternal border suggested an arteriovenous communication most likely involving the coronary system. For this reason, venous catheterization was performed and the lesion was demonstrated.

It is apparent that the group of patients having a continuous murmur in the area common to patent ductus will for the most part evade accurate diagnosis until thoracotomy is performed. On the other hand, when the murmur is in an atypical location, coronary arteriovenous fistula should be considered in the differential diagnosis. When these findings are present venous catheterization may be of important diagnostic value. If the communication is between the coronary artery and the coronary venous drainage, sampling from the coronary sinus or its more distal tributaries will reveal an elevation in oxygen content of the blood. If the arterial communication is with the right ventricle or pulmonary artery, it is unlikely that this procedure will be of diagnostic aid. In the former instance the findings may be identical to those of

TABLE IV

HEMODYNAMIC DATA ON FOUR PATIENTS WITH CORONARY ARTERIOVENOUS FISTULA

Author	Case	Diagnosis	Cardiac Output L./min.	Cardiac Index L./M.²/min.	Pulmonary Flow		Left to Right Shunt		Pressures (mm./Hg)					
									Pulmonary Artery		Right Ventricular	Right Atrial	Brachial	
					L./min.	L./M.²/min.	L./min.	L./M.²/min.	Systolic/Diastolic	Mean	Systolic Diastolic/	Mean	Systolic/Diastolic	Mean
Davison et al. [9]	9	Coronary artery to sinus	3.1	2.1	7.1	4.7	3.9	2.6	75/25	45	76/14	14	140/60	88
Davis et al. [11]	11	Coronary artery to right ventricular outflow tract	4.9	...	6.6	....	1.7	...	19/9	..	22/2	2	114/68	..
Authors' Case I, E. L.	12	Probable coronary artery to middle cardiac vein	5.9	5.6	11.1	11.7	5.2	5.5	30/13	21	30/6	4	130/84	..
Authors' Case II, P. S.	13	Right coronary artery to pulmonary artery	5.0	4.1	7.0	4.1	2.0	1.2	33/17	25	27/7	11	102/65	75

Note: Zero point of reference not given by Davis. The zero point in Davison's case was the sternal angle, and in authors' two cases was the skin of the back.

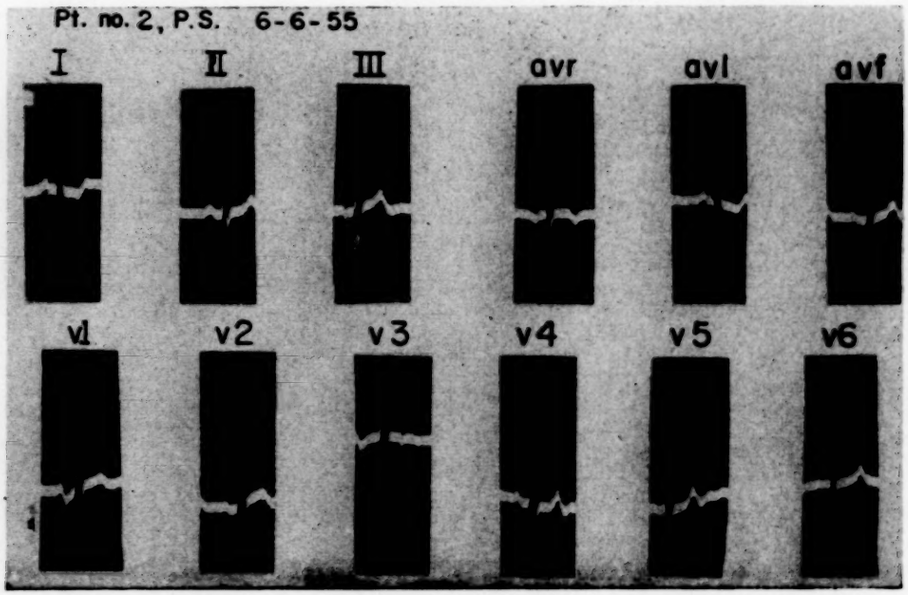


FIG. 5. Case II. Electrocardiogram. The frontal axis is about 0 degrees. ST and T wave abnormalities are present in standard lead I and AVL.

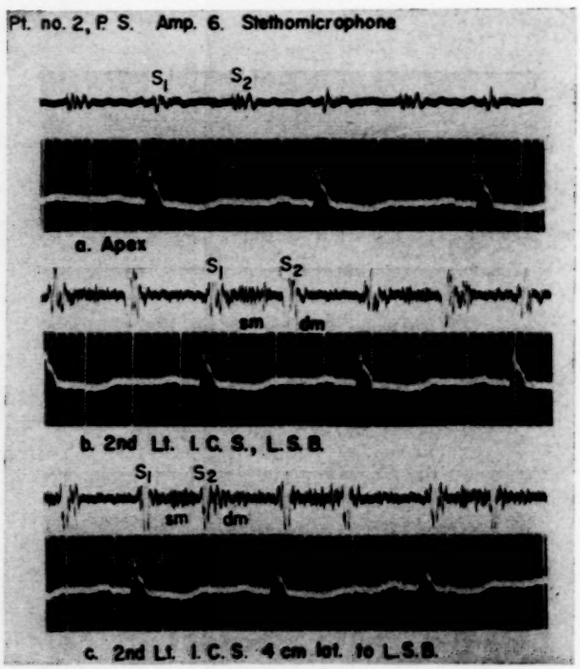


FIG. 6. Case II. Phonocardiogram demonstrating a continuous murmur at and just lateral to the pulmonic area.

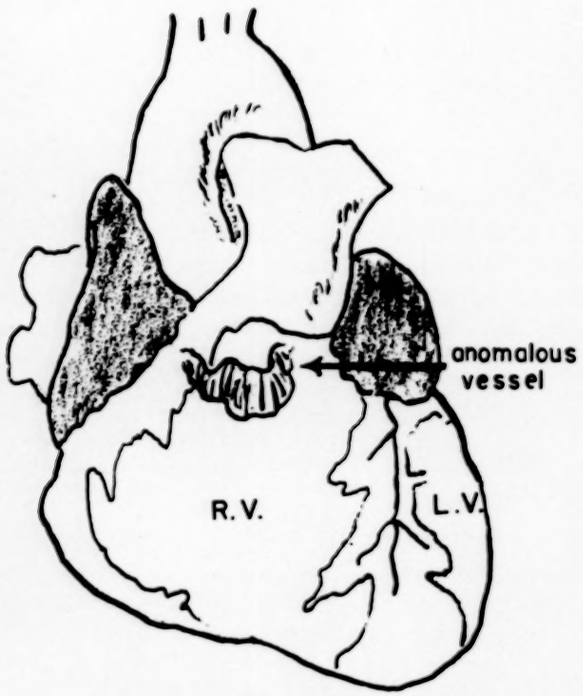


FIG. 7. Case II. Sketch of heart as seen at operation. The large anomalous channel came from the right coronary artery and disappeared into the right ventricular substance just proximal to the pulmonary valve.

a ventricular septal defect or patent ductus with pulmonic insufficiency. When the communication is with the pulmonary artery, an increase in the blood oxygen content of the main pulmonary artery would not distinguish between this lesion and a patent ductus. Although venous catheterization is of value in diagnosis and functional assessment of coronary arteriovenous fistula, the procedure is not without some hazard in this lesion. Pathologic study of the cases in-

cluded in this report show that the dilated anomalous channels are sometimes no more than thin walled sacs. It is not inconceivable that forceful manipulation of the catheter might result in penetration of the wall. Great care should therefore be exercised when the catheter enters the coronary venous system.

Prognosis: Of the six necropsy reports there is sufficient explanation for the cause of death in five cases without incriminating the coronary arteriovenous fistula. Three patients, Cases 7, 1 and 3 died of metastatic malignancy at ages seventy-six, fifty-four and forty-three, respectively. Löwenheim's patient, age sixty-two had significant hypertension, an adequate explanation for the congestive failure. Colbeck's patient survived without cardiovascular symptoms to age eighty-five, at which time congestive failure developed. In the case of Brown and Burnett, acute laryngotracheobronchitis was the cause of death. Lack of any other cardiovascular abnormalities in the case of Davison et al. favors the coronary arteriovenous communication as the most important factor in this patient's rapid downhill course of congestive failure and death.

Of the seven living patients six have had thoracotomies. In three no attempt was made to correct the anomalous communication, and in three a corrective procedure was performed. All of the living patients were well at the time they were reported, and our two patients have remained asymptomatic. Significant cardiac symptomatology was described preoperatively by Biörck and also by Sondergaard in their two patients. Sondergaard describes disappearance of symptoms, regression of heart size, and absence of a left to right shunt as demonstrated by venous catheterization three months after corrective surgery. Biörck's patient, evaluated four months after ligation of the anomalous vessel, had improved symptomatically. A third patient reported by Davis had no cardiovascular symptoms before corrective surgery.

Two potential complications of this lesion are worth mentioning at this point. Subacute bacterial endarteritis was not encountered in any of the case reports, but since it is not infrequently seen in patent ductus and may occur in peripheral arteriovenous fistulas, it might be expected to occur in this lesion. It should be noted also that in other congenital cardiovascular anomalies in which pulmonary blood flow is increased, the vascular resistance of the lesser circulation may become elevated, and it has been suggested that a high pulmonary flow is sometimes responsible for the increased resistance [*18,19*]. If this be the case, then it might be expected that pulmonary vascular obstruction would occur in some of these patients. Based on necropsy findings of the lungs there is no evidence that this obtains, but in the case reported by Davison et al. physiologic data suggest that pulmonary resistance was moderately increased.

Treatment: No conclusions can be drawn concerning the proper management of a coronary arteriovenous fistula. Because of its apparently good prognosis in the asymptomatic patient, corrective surgery might be reasonably deferred in this group. As mentioned before, a certain number of patients will likely not have a correct diagnosis before the surgeon has opened the chest. Whether or not correction should be carried out at that time will depend upon the surgeon's estimate of the operability of the lesion as well as the preoperative clinical estimate of the functional significance of the lesion. In this respect the more cogent considerations should be: (1) symptomatology, (2) presence or absence of ventricular hypertrophy by electrocardiogram and (3) size of the heart and pulmonary artery as well as degree of vascularity of the lungs by x-ray. If the diagnosis is made by venous catheterization, physiologic data will be a useful guide in the course to follow.

SUMMARY

1. Two cases of congenital arteriovenous communication of the coronary system studied by venous catheterization are presented.

2. The clinical features and the effects of this lesion on the circulation are discussed.

3. Twelve cases of this anomaly found in the literature are reviewed.

Acknowledgment: We are indebted to Miss Caroline Thalheimer for her technical assistance and to Miss Violet Peters for her help in preparing the manuscript.

ADDENDUM

Dr. Edward F. Bland of the Department of Cardiology of the Massachusetts General Hospital granted us permission to examine the record of the patient reported by Paul et al. in 1949. This boy is now sixteen years of age, has grown normally, has had no cardiovascular symptoms and leads a completely normal life.

REFERENCES

1. Halpert, B. Arterio-venous communication between the right coronary artery and the coronary sinus. *Heart*, 15: 129, 1930.
2. Löwenheim, I. Eine seltene Missbildung der Coronärgefasse. *Frankfurt. Ztschr. Path.*, 43: 63, 1932.
3. Harris, P. N. Aneurysmal dilatation of cardiac coronary arteries. *Am. J. Path.*, 13: 89, 1937.
4. Biörck, G. and Crafoord, C. Arteriovenous aneurysm on the pulmonary artery simulating patent ductus arteriosus Botalli. *Thorax*, 2: 65, 1947.
5. Paul, O., Sweet, R. H. and White, P. D. Coronary arterio-venous fistula. *Am. Heart J.*, 37: 441, 1949.
6. Brown, R. C. and Burnett, J. D. Anomalous channel between aorta and right ventricle. *Pediatrics*, 3: 597, 1949.
7. Baylis, J. H. and Campbell, M. An unusual cause for a continuous murmur. *Guy's Hosp. Rep.*, 101: 174, 1952.
8. Colbeck, J. C. and Shaw, J. M. Coronary aneurysm with arterio-venous fistula. *Am. Heart J.*, 48: 270, 1954.
9. Davison, R. H., McCracken, B. H. and McIlveen, D. J. S. Congenital coronary arteriovenous aneurysm. *Brit. Heart J.*, 17: 569, 1955.
10. Sondergaard, T. Henry Ford Hospital, International Symposium on Cardiovascular Surgery. Philadelphia, 1955. W. B. Saunders Co.
11. Davis, C., Jr., Dillon, R. F., Fell, E. H. and Gasul, B. M. Anomalous coronary artery simulating patent ductus arteriosus. *J. A. M. A.*, 160: 1047, 1956.
12. White, P. D. Heart Disease. New York, 1951. The Macmillan Co.
13. Jones, A. M. and Langley, E. A. Aortic sinus aneurysm. *Brit. Heart J.*, 11: 325, 1949.
14. Rushmer, R. M. Cardiac Diagnosis. Philadelphia, London, 1955. W. B. Saunders Co.
15. Kjellberg, S. R., Mannheimer, E., Rudhe, U. and Jonsson, B. Diagnosis of Congenital Heart Disease. Chicago, 1955. Year Book Publishers, Inc.
16. Taussig, H. B. Congenital Malformations of the Heart. Commonwealth Fund, New York, 1947.
17. Kieth, J. D., Rowen, R. D., Vlad, P. and O'Hanley, J. H. Complete anomalous pulmonary venous drainage. *Am. J. Med.*, 16: 23, 1954.
18. Swan, H. J. G., Zapata-Diaz, J., Burchell, H. B. and Wood, E. H. Pulmonary hypertension in congenital heart disease. *Am. J. Med.*, 16: 12, 1954.
19. Blount, S. G., Jr., Mueller, H. and McCord, M. C. Ventricular septal defect, clinical and hemodynamic patterns. *Am. J. Med.*, 18: 871, 1955.

The Electrocardiogram in Atrial Septal Defect*

A Study of Twenty-four Cases, with Observations on the RSR'-V1 Pattern

W. R. MILNOR, M.D. *and* C. A. BERTRAND, M.D.

Baltimore, Maryland

THE development of surgical methods for repairing congenital defects of the interatrial septum makes accurate diagnosis of the presence and exact location of such lesions a matter of practical importance. Although numerous authors[1,3,5,11,15] have described the electrocardiographic findings in cases of atrial septal defect, there are relatively few reports which include both anatomic proof of the diagnosis and complete electrocardiographic observations with multiple precordial leads, and little attention has been given to the location of the defect in the septum. These facts led us to undertake a study of the electrocardiogram in atrial septal defect based on a group of cases in which the diagnosis was confirmed by autopsy or surgical exploration.

MATERIAL

Twenty-four patients form the basis of the present report; the pertinent data are given in Table 1. In all cases, cardiac catheterization was performed, electrocardiograms with at least three limb leads and three precordial leads were recorded, and the diagnosis of atrial septal defect, uncomplicated by other lesions except auricular or ventricular hypertrophy or anomalies of the atrio-ventricular valves, was confirmed by autopsy (seven cases) or by surgical exploration (seventeen cases). These include all patients over twelve months of age examined at the Johns Hopkins Hospital from 1950 to 1955, inclusive, which satisfied the requirements stated, and one patient (Case 5) examined at the Clinical Center, National Heart Institute, National Institutes of Health, Bethesda, Maryland. Cases of atrial septal defect with complicating lesions other than those specified heretofore were excluded from this series, with the single exception of Case 3 in which a small and probably functionally insignificant patent ductus arteriosus was ligated when the patient was fourteen months old, nine years prior to the observations reported here.

In six of the autopsy cases (Cases 1, 2, 3, 4, 6, 20) surgical repair of the defect had previously been attempted.

Since atrial septal defects are sometimes compatible with a long and asymptomatic life,[7] it should be pointed out that in all the cases described here symptoms attributable to the cardiac anomaly had developed and our conclusions therefore do not necessarily apply to less severe or asymptomatic cases.

METHODS

Anatomic Criteria. In five of the autopsy cases the heart was re-examined by one of the authors; in the remaining cases information was obtained from the detailed report of the pathologist or from the surgeon. In each of the autopsy cases an increase in the size of a ventricle was accompanied by an increase in the wall thickness.

The absence of complicating lesions is, of course, less certain in the surgical than in the autopsy cases but every effort was made at the time of operation to rule out additional abnormalities.

The cases were divided into two groups on the basis of the site and character of the septal defect. Defects which were adjacent to the endocardial cushion between the tricuspid and mitral valves, with no remaining rim of septum along this edge, were designated "persistent ostium† primum." All other defects

† The word "foramen" (= Latin "hole") has been favored by anatomists, and is perhaps a more exact term for describing an opening in a septum between two chambers, but "ostium" (= Latin "door") has gained wide clinical use.

* From the Department of Medicine, The Johns Hopkins University School of Medicine and Hospital, Baltimore, Maryland. This work was supported in part by a research grant (H-328) from the National Heart Institute of the National Institutes of Health, United States Public Health Service.

TABLE I

SUMMARY OF DATA ON TWENTY-FOUR CASES OF UNCOMPLICATED ATRIAL SEPTAL DEFECT CONFIRMED BY AUTOPSY OR OPERATION

Case No. and Initials	Age (yr.)	Sex	Catheterization Data		Electrocardiographic Data								Anatomic Data					
			Pulmonary Artery Pressure (mm. Hg)*	Ratio Pulmonic / Systemic Flow	Ventricular Rate (per min.)	Rhythm†	PR Interval (sec.)‡	QRS Duration (sec.)	Mean Frontal QRS Axis	V1 Pattern	Amplitude of R or R′ − V1 (mv.)§	Evidence of Ventricular Hypertrophy¶	Source of Information**	Location of Defect	Size of Defect (cm.)	Mitral Valve	Right Ventricular Enlargement††	Left Ventricular Enlargement††
Cases of Persistent Ostium Primum																		
1, R. W.	4	M	(37/0)	4.5	120	NSR	*0.19*	0.09	−45°	rsR′s′	0.6	L. and Rt.	A	Low	1.5 × 2	Cleft	+	+
2, M. D.	5	M	34/11	3.4	115	NSR	*0.22*	0.09	−48°	rSR′	0.9	L. and Rt.	A	Low	4 × 4	Cleft	+	+
3, J. G.	10	M	34/7	3.8	96	NSR	*0.20*	0.10	−58°	rsR′s′	0.9	L. and Rt.	A	Low	3 × 3	Cleft	+	+
4 Z. O.	26	F	108/39	1.7	85	NSR	*0.22*	0.07	+116°	Rs	0.8	Rt.	A	Low	2 × 4	Cleft	+	0
5, M. L.	37	F	60/30	3.8	70	AF	....	0.10	+110°	rsR′	0.5	Rt.	O	Low	3 × 3	Normal	..	..
6, K. B.	52	F	49/13	4.6	74	AF	....	0.14	−74°	rsR′	0.5	O ?	A	Low	3 × 3	Normal	+	0
Cases of Persistent Ostium Secundum																		
7, W. V.	6	M	39/13	4.3	116	WP	....	0.08	+92°	rsR′	1.1	Rt.	O	High	4 × 3	Normal	..	..
8, J. J.	7	F	(90/4)	4.6	125	NSR	0.18	0.08	−102°	rsR′	1.7	Rt.	O	Mid	2 × 2	Normal	..	..
9, M. M.	8	F	57/31	4.0	120	WP	....	0.07	+110°	R	1.0	Rt.	O	Mid	4 × 4	Normal	..	..
10, H. W.	9	F	(34/4)	3.2	120	NSR	0.14	0.08	+118°	rsR′s′	1.9	Rt.	O	High	2 × 2	Normal	..	..
11, K. N.	10	M	30/15	3.7	106	NSR	0.12	0.10	+118°	rsR′	0.8	Rt.	O	Mid	5 × 5	Normal	..	..
12, N. M.	12	F	46/12	3.6	112	NSR	*0.22*	0.07	+126°	R	1.1	Rt.	O	High	2.5 × 2.5	Normal	..	..
13, E. S.	23	F	95/23	2.1	108	NSR	0.12	0.06	+116°	R	1.9	Rt.	A	Mid	2 × 2	Normal	+	0
14, L. W.	24	F	48/18	4.8	92	NSR	0.20	0.09	+120°	R	0.9	Rt.	O	Mid	5 × 3	Normal	..	..
15, R. S.	27	F	24/10	4.6	84	NSR	0.19	0.07	+130°	R	0.5	Rt.	O	High	.....	Normal	..	..
16, D. S.	28	M	90/38	1.7	98	NSR	0.20	0.12	+122°	rsR′	1.5	Rt.	O	Mid	.....	Normal	..	..
17, M. A.	33	F	60/28	2.5	85	NSR	0.18	0.06	+128°	Rs	0.8	Rt.	O	High	3 × 3	Normal	..	..
18, H. W.	34	F	45/6	4.0	88	NSR	*0.21*	0.11	+110°	rsR′	1.0	Rt.	O	Mid	.....	Normal	..	..
19, S. M.	37	F	64/13	1.6	75	NSR	0.18	0.06	+118°	R	1.4	Rt.	O	High	2 × 4	Normal	..	..
20, M. S.	38	F	58/12	6.2	85	NSR	0.16	0.11	+5°	rsR′	0.8	Rt.	A	Mid	4 × 4	Normal	+	0
21, E. R.	39	F	74/31	1.4	78	NSR	0.20	0.06	+112°	Rs	0.5	Rt.	O	High	3 × 3	Normal	..	..
22, F. N.	39	F	26/4	1.3	70	NSR	0.20	0.10	+92°	rsR′	0.9	Rt.	O	High	Multiple	Normal	..	..
23, D. A.	44	F	49/20	1.5	102	NSR	0.14	0.11	+82°	rsR′	1.1	Rt.	O	Mid	2 × 3.5	Normal	..	..
24, O. C.	45	F	38/9	4.4	75	AF	....	0.11	+104°	rsR′	0.8	Rt.	O	Mid	2 × 3	Normal	..	..

* Figures in parentheses are right ventricular pressure, in cases where pulmonary artery pressure not recorded.

† NSR = normal sinus rhythm; WP = wandering supraventricular pacemaker; AF = atrial fibrillation.

‡ Italicized figures indicate prolongation beyond normal limits for age and heart rate.

§ Amplitude given is that of largest positive deflection in lead V1. In each case with an R′, R′ was greater than R.

¶ See criteria for electrocardiographic diagnosis of ventricular hypertrophy in text.

** A = autopsy; O = operation. Surgical repair of the atrial septal defect was performed at the Clinical Center of the National Heart Institute in Case 5; at the Children's Medical Center, Boston, in Case 3, and at the Johns Hopkins Hospital in the remaining operative cases.

†† + = presence, 0 = absence of enlargement or hypertrophy, in autopsy cases only.

were called "persistent ostium secundum," and further characterized by their position in the septum as "high" (cephalad) or "mid-septal."

Such a distinction is not always embryologically accurate,[9] particularly in the case of large or multiple defects where both foramina and both septa are probably abnormal. It does have practical value, however, because surgical repair of the defect is technically very difficult if no rim of tissue remains above the intervalvular endocardial cushion. Although in many cases (Cases 1, 2, 3, 4) an anomaly of the mitral or tricuspid valve accompanies the "ostium primum" type of defect,[14,16] this is not invariably true and is not here included as part of the definition.

In Case 9, although the surgeon believed a very narrow ridge of atrial septum still remained at the lower edge of the defect, he could not be certain and it may not be correct to list this case as a persistent ostium secundum.

In Case 1 there was a wide and continuous cleft in the aortic leaflet of the mitral valve and the septal leaflet of the tricuspid valve which must of necessity have allowed regurgitation through both valves. In Cases 2, 3 and 4 only the mitral valve showed a cleft, and it was impossible to tell from examination of the valve alone whether or not it had been functionally insufficient. The presence of left ventricular hypertrophy in Cases 2 and 3 was regarded as evidence that mitral insufficiency had been present.

Electrocardiography. The data in Table 1 refer to the latest electrocardiogram prior to operation or, if no operation was performed, to the latest available record. Electrocardiograms had been taken within six months of death in the autopsy cases and not more than two months before operation in the others.

Routine electrocardiograms, recorded at standard paper speed of 25 mm. per second on either a single-channel photographic or two-channel "direct-writing" instrument, were used in most instances. In nine cases electrocardiograms similar to those shown in Figures 1 and 2, with simultaneous multiple-lead records at faster paper speeds and higher frequency response, were also available. The vectorcardiogram in Figure 2 was recorded from a bipolar cubical lead system in use in this laboratory,[12] in which the x, y and z axes share one common electrode on the right upper back.

The normal limits for PR interval and P wave amplitude published by the New York Heart Association[13] were used for patients over seventeen years of age and those published by Ziegler[18] for younger patients.

The mean frontal plane QRS axis was calculated from the standard limb leads and the nomogram of Carter, Richter and Greene.[8] Axes with positive values from 0° to +90° or negative values from 0° to −10° were considered to be normal. The area of "left axis deviation" was defined as −11 to −90°, and "right axis deviation" as the two quadrants from +91° to 180° and −91° to 180°.

Electrocardiograms were interpreted as showing evidence of right ventricular hypertrophy when the R/S ratio in lead V1 was greater than 1.0, the maximum amplitude of R or R′ in lead V1 was greater than 0.5 millivolts, and the QRS duration was less than 0.12 seconds. These criteria are derived from an unpublished study in this laboratory, described below in more detail. Right axis deviation, absence of the normal "precordial transition" and a QRS-T angle approaching 180° usually accompanied this pattern but were not required for the electrocardiographic diagnosis of "right ventricular hypertrophy."

The term "RSR′-V1 pattern" is used to describe this QRS complex configuration in lead V1, regardless of duration, and includes instances where an S′ is also present in this lead.

A maximum R wave amplitude of more than 2.2 millivolts in lead 1, or more than 2.5 millivolts in lead V6, was interpreted as electrocardiographic evidence of left ventricular hypertrophy.

Measurements of the "intrinsicoid deflection time" were not used. In our opinion the use of the R-peak in leads from the body surface as an indication of the time of arrival of the depolarization wave over one ventricle is unsound in theory and gives no diagnostic information in practice that is not provided by measurement of the total QRS duration.

Cardiac Catheterization. Data were obtained during routine diagnostic catheterization. The right ventricular or pulmonary artery pressures given in Table 1 were measured during mid-inspiration. The zero level for pressure readings was a plane parallel with the top of the fluoroscope table, at a distance above it equal to two-thirds the maximum sagittal diameter of the patient's chest at the second costo-chondral junction. The ratio of pulmonary artery to systemic blood flow is given instead of absolute flow rate because the oxygen consumption measurement needed for calculation of the latter was not available in every instance. The net shunt was from left to right in each case. At the time of catheterization peripheral arterial oxygen saturation was 80 per cent in Case 18, 91 per cent in Case 4, and 94 per cent or more in all other cases.

RESULTS AND DISCUSSION

Persistent Ostium Primum versus Persistent Ostium Secundum. Cases 1, 2 and 3 form a homogeneous group pathologically, and can be distinguished from the other cases electrocardiographically. All three patients had a persistent ostium primum, a cleft in the aortic leaflet of the mitral valve and hypertrophy of both left and right ventricles. Each one showed left axis deviation and signs of combined left and right ventricular hypertrophy in the electrocardiogram. The record shown in Figure 3 is typical.

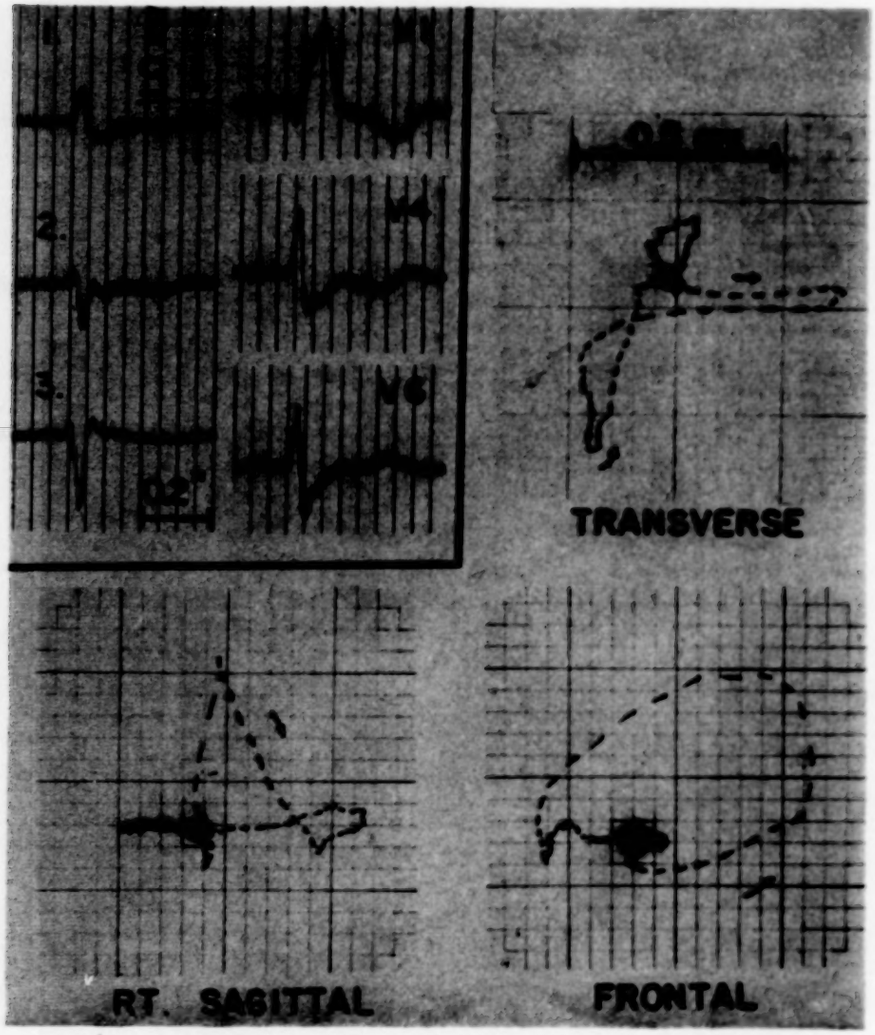


FIG. 1. Case 6. This patient, a fifty-two year old woman, was the oldest in the present series. Vectorcardiograms were recorded from a bipolar, cubical lead system, with an electrode common to the x, y and z axes on the right upper back.[12] Timing of the vectorcardiogram loops is provided by interruption of the tracing at intervals of 2.5 milliseconds. The transverse view is oriented as if the patient's back were toward the top of the page. Electrocardiogram and vectorcardiogram interpretation: atrial fibrillation, complete right bundle branch block (QRS duration 0.14 second). The early, non-delayed portion of the QRS complex shows left axis deviation. The later portions of the QRS complex are oriented toward the right anterior chest and there is marked slowing of the trace at the most anterior part of this late "appendage." The speed of the cathode ray spot during the QRS complex is a function of the rate of change of direction and magnitude of the net vector sum of electrical forces produced by ventricular depolarization. It is therefore not necessarily related to the speed with which the depolarization wave travels through any particular area of the myocardium, but slowing of this kind is usually found in cases which show the ECG pattern defined as complete bundle branch block. We cannot agree with Grishman[10] that this kind of figure 8 contour of the transverse QRS loop is diagnostic of right ventricular hypertrophy, regardless of QRS duration, since in our experience this same configuration, with a QRS duration greater than 0.12 second, is often found in cases of chronic coronary disease and myocardial infarction. In such cases the amplitude of R′-V1 in the electrocardiogram may be just as great as in cases of right ventricular hypertrophy. Autopsy findings: atrial septal defect (persistent ostium primum); normal mitral and tricuspid valves; right atrial enlargement; right ventricular hypertrophy; coronary arteries showed atherosclerosis with extreme narrowing of the left anterior descending artery and small areas of fibrosis scattered through the left ventricular myocardium.

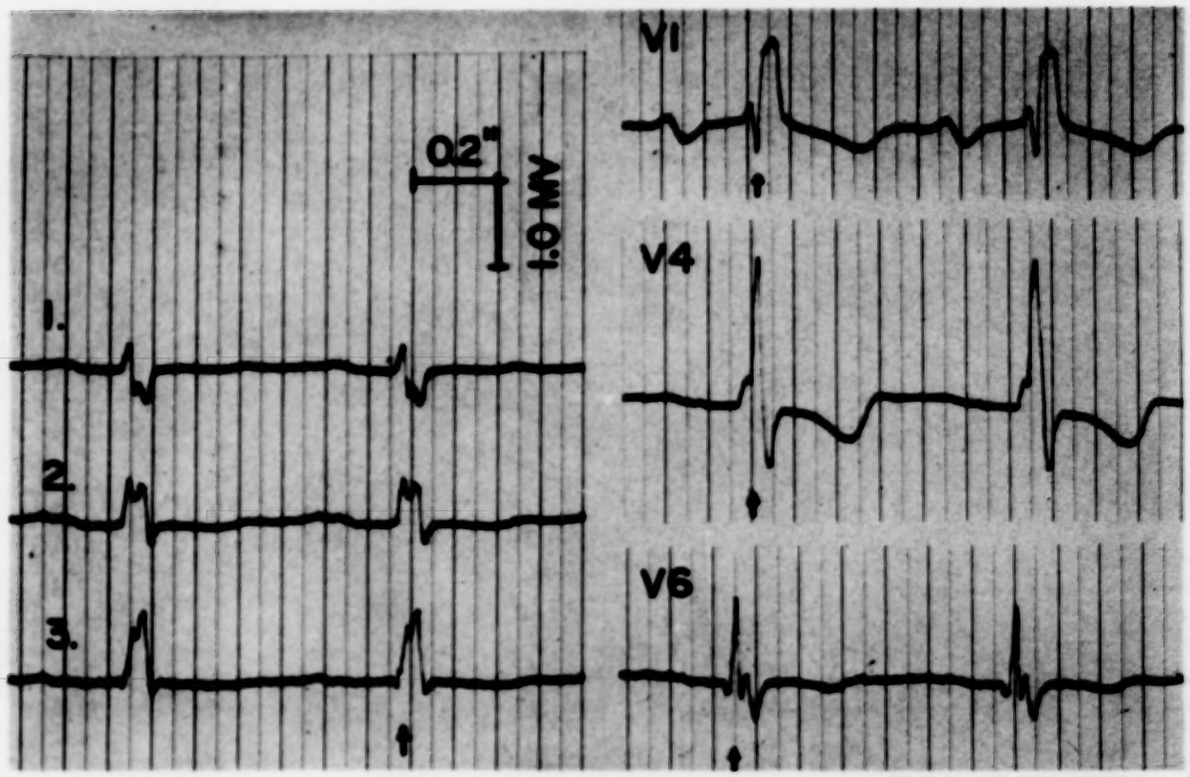


FIG. 2. Case 18. This patient was a thirty-four year old woman. Arrows indicate time of peak of R wave in lead 1. Electrocardiogram interpretation: PR interval at upper limit of normal; RSR′-V1 pattern with QRS duration of 0.09 second; right axis deviation; right ventricular hypertrophy. Operative findings: atrial septal defect (persistent ostium secundum); normal mitral and tricuspid valves; enlarged right atrium and right ventricle. Similar electrocardiographic findings, with QRS duration less than 0.12 second, were present in nine of the twenty cases in this series with atrial septal defects and no abnormality of mitral or tricuspid valves.

In the remaining twenty-one cases, in which there was right ventricular but no left ventricular enlargement anatomically, the electrocardiogram showed right axis deviation and right ventricular hypertrophy in eighteen cases, normal axis and right ventricular hypertrophy in one case, complete right bundle branch block with left axis deviation in one case and complete right bundle branch block with right axis deviation in one case.

These findings suggest that left axis deviation and signs of left ventricular hypertrophy in a patient with an atrial septal defect usually indicate a persistent ostium primum with cleft mitral valve and mitral insufficiency. The mitral valve may sometimes be competent even though a recognizable cleft persists in the aortic leaflet, as illustrated by Case 4 in which there was no evidence of left ventricular hypertrophy at autopsy. The electrocardiogram in this case (Fig. 4) showed no sign of left ventricular hypertrophy. A persistent atrioventricular cleft sometimes extends into one leaflet of the tricuspid valve as well, as in Case 1, but this apparently does not modify the electrocardiogram.

It is significant that in these three cases of persistent ostium primum with accompanying anomalies of the A-V valves, the patients had severe symptoms before the age of ten years. Rogers and Edwards[14] have pointed out that early death is common with such a combination of lesions.

The association between left axis deviation and persistent ostium primum, in contrast to the usual right axis deviation in other atrial septal defects, has been commented on in clinical practice by Dr. Helen Taussig in the Harriet Lane Home Cardiac Clinic of the Johns Hopkins Hospital since 1953, and attention was called to the diagnostic importance of this finding by Dr. S. G. Blount in his discussion of a paper at the Second World Congress of Cardiology in September 1954. Our data confirm these observations, and show that the electrocardiographic signs of left ventricular hypertrophy are not due to the atrial defect itself, but to mitral

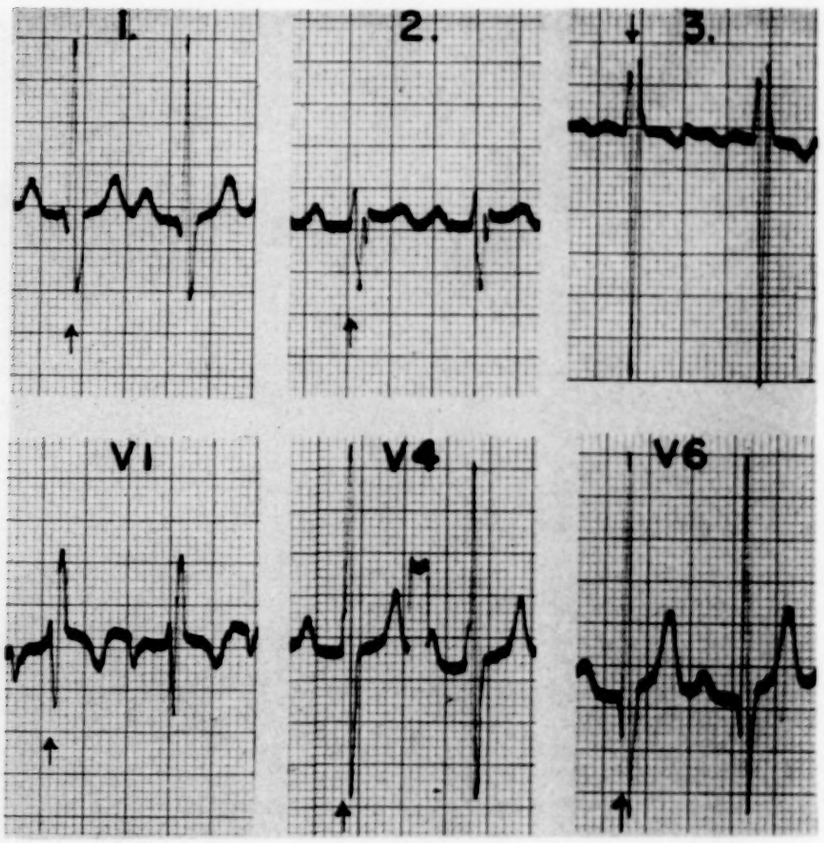


FIG. 3. Case 2. This patient was a five-year old boy. Arrows indicate the time of the peak of the R wave in lead 1 and synchronous points in other leads. Standardization in all leads is the same as that shown in lead V4. Paper speed 25 mm. (25 small squares) per second. Electrocardiogram interpretation: prolonged PR interval; left axis deviation; RSR′-V1 pattern; combined right and left ventricular enlargement. Autopsy findings: atrial septal defect (persistent ostium primum); cleft aortic leaflet of the mitral valve; normal tricuspid valve; right and left ventricular hypertrophy; dilated right atrium. The left ventricular hypertrophy was presumably due to insufficiency of the anomalous mitral valve.

insufficiency. When the mitral valve is competent, there is at present no reliable way of differentiating between persistent ostium primum and persistent ostium secundum.

Although patients with a persistent ostium primum and a competent mitral valve usually show right axis deviation in the electrocardiogram (Cases 4 and 5), exceptions to this rule may occur, as illustrated by Case 6. (Fig. 1.) The QRS complex in this instance was greatly prolonged in duration (0.14″) and showed the electrocardiographic pattern of complete right bundle branch block. The vectorcardiogram showed the late, slow, terminal "appendage" to the QRS complex usually seen with this electrocardiographic pattern, and left axis deviation of the early QRS complex. At autopsy there was considerable coronary atherosclerosis, with extreme narrowing of the left anterior descending artery, and small areas of fibrosis scattered diffusely through the left ventricular muscle. The left ventricle was slightly dilated but not hypertrophied. In this case, therefore, the left axis deviation and bundle branch block may be related to chronic coronary insufficiency.

The RSR′-V1 Pattern: Incidence. In fifteen cases there was an RSR′ pattern in lead V1, including three patients with a final S′. The QRS duration was 0.09 second or less in five cases, greater than 0.09 second but less than 0.12 second in eight cases, and 0.12 second or more in two cases.

Several authors have commented on the high incidence of "right bundle branch block" with atrial septal defects.[1,5,15] The present study confirms the observation that an RSR′-V1

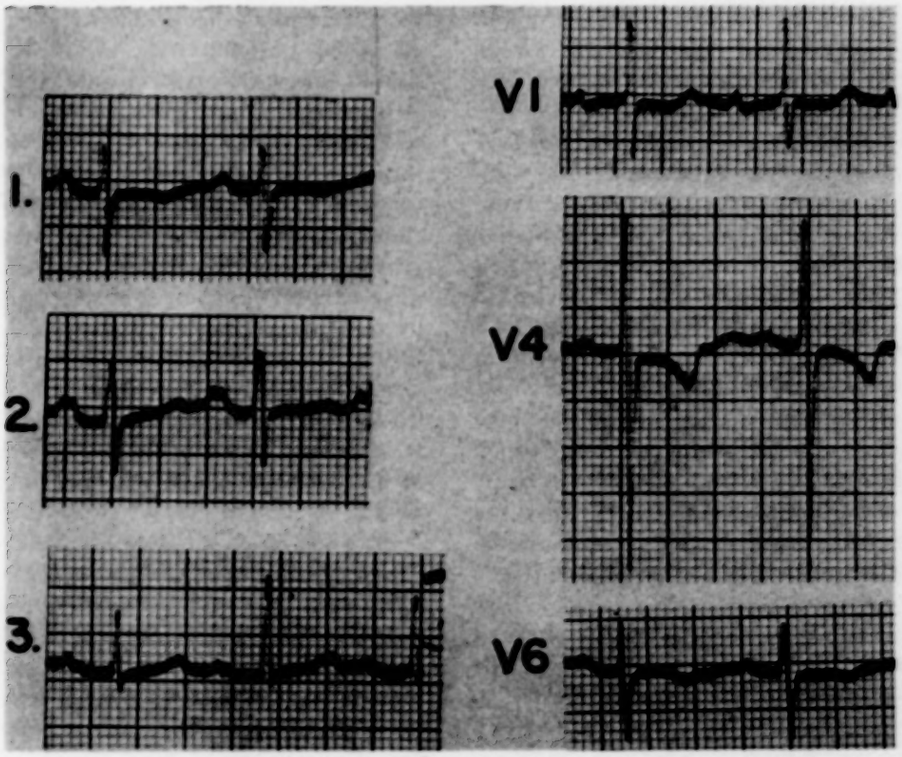


FIG. 4. Case 4. This patient was a twenty-six year old woman. Standardization in all leads is the same as that shown in lead 3. Paper speed 25 mm. per second. Electrocardiogram interpretation: prolonged PR interval; right axis deviation; right ventricular hypertrophy. Autopsy findings: atrial septal defect (persistent ostium primum); normal mitral and tricuspid valves; right atrial dilatation; right ventricular hypertrophy.

pattern occurs frequently with this disease (63 per cent of our twenty-four cases) but it should be noted that "complete right bundle branch block," with QRS duration prolonged beyond normal limits, appeared in only two of our patients, aged twenty-eight and fifty-two years. Whether or not the RSR′-V1 pattern with QRS duration *less* than 0.12 second is necessarily associated with conduction delay in the branches of the bundle of His is a debatable question, to be discussed in more detail subsequently.

Since nine patients (37 per cent) in our series did not show the RSR′-V1 pattern, we cannot agree with Barber, Magidson and Wood that " . . . the diagnosis of A. S. D. is almost untenable in the absence of partial or complete R.B.B.B."[1]

The RSR′-V1 Pattern: Significance. It seems possible that the RSR′-V1 pattern sometimes represents an intermediate stage in the development of electrocardiographic signs of right ventricular hypertrophy, and that it is not necessarily associated with localized conduction delay. Its frequent association with right ventricular enlargement in a variety of diseases, sometimes with entirely normal QRS duration, supports this hypothesis. We have found the RSR′-V1 pattern, with QRS duration less than 0.12 second, in 5 per cent of one hundred fifty patients with rheumatic mitral stenosis, 24 per cent of twenty-five patients with isolated pulmonic stenosis, and 19 per cent of twenty-seven patients with chronic cor pulmonale. In these same groups the incidence of the RSR′-V1 pattern with QRS duration of 0.12 second or more was: mitral stenosis, 1 per cent; pulmonic stenosis, 12 per cent; cor pulmonale, 4 per cent.

Further support for this concept is given by occasional cases of pulmonic stenosis in which the V1 contour changes from a tall R to an RSR′ after the stenosis has been relieved surgically. Blount, McCord, Mueller and Swan have described three such cases[4] and we have observed two others.

Most publications concerned with the electrocardiographic diagnosis of right ventricular hypertrophy fail to give criteria which apply when an RSR′-V1 is present. Usually, this

pattern is attributed to delayed conduction and termed "incomplete right bundle branch block"[2,17] when the QRS duration is from 0.10 second to 0.12 second.

From an unpublished investigation of this subject we have tentatively concluded that right ventricular hypertrophy is usually present when: (a) the tallest R wave in lead V1 is 0.5 millivolts or more in amplitude; (b) the ratio of the maximum amplitudes of the tallest R and deepest S in lead V1 is greater than 1.0; and (c) the QRS duration is less than 0.12 second. These criteria apply to QR, R, RS, RSR′, RSR′S′ or other QRS contours in lead V1. Although we have not studied normal patients under the age of ten years, the normal standards of Ziegler[18] indicate that the criteria indicated probably apply to children over six years of age as well as to adults. They are naturally not applicable in the presence of dextrocardia.

These conclusions are derived from a study of fifty-eight consecutive patients examined in the Heart Station of the Johns Hopkins Hospital, in whom the electrocardiogram satisfied the three requirements given, and sufficient information (excluding the electrocardiogram) was available to establish a clinical diagnosis. Fifty-one (88 per cent) of these patients showed definite clinical evidence of right ventricular enlargement due to cardiac or pulmonary disease; seven (12 per cent) had evidence of coronary artery disease and no right ventricular enlargement. No patients with normal hearts were found in this group.

In a separate study of one hundred three normal subjects aged ten to seventy years, four subjects were found with an RSR′-V1, but the R′ amplitude was less than 0.2 millivolts and the R/S ratio was 0.3 or less.

When the QRS duration was 0.12 second or greater these criteria for the electrocardiographic diagnosis of right ventricular hypertrophy were not valid. In forty cases which met criteria (a) and (b) but had QRS durations greater than 0.12 second, thirty-three patients (83 per cent) had definite clinical evidence of coronary artery disease and no indication of right ventricular hypertrophy.

These criteria have been found to be useful clinically but they cast no light on the possible relation between the RSR′-V1 pattern and delayed intraventricular conduction. If this pattern were due to right ventricular hypertrophy alone, with no conduction disturbance, then measurements of the QRS duration in a group of patients with an RSR′-V1 pattern should show the same range and distribution as in normal subjects, but we have not found this to be true. Measurements of the QRS duration in a series of 103 normal subjects in this laboratory gave an average of 0.086 second, with a standard deviation of ±0.012 second. In a group of patients with electrocardiographic signs of right ventricular hypertrophy as defined herein (and therefore excluding patients with QRS duration of 0.12 second or more), we found QRS durations greater than 0.09 but less than 0.12 second in 31 per cent of thirty-two patients who showed an R′ in V1, and in only 11 per cent of forty-four patients who did not show an R′ in V1.

This increased incidence of QRS durations in the "high normal" range in patients with an RSR′-V1 and right ventricular hypertrophy suggests that conduction delay must play a part in the pathogenesis of the RSR′-V1 pattern in at least some instances, but in the absence of direct evidence there seems no justification for assigning the site of the conduction delay to the "bundle branches." The question is further complicated by the fact that even a normal QRS duration does not guarantee the absence of conduction disturbance, as shown by two cases reported by Braunwald, Fishman and Cournand[6] in which definite delay in right ventricular contraction was demonstrated, although the QRS duration was 0.08 second.

Records of the first appearance and progressive development of the RSR′ and right ventricular hypertrophy patterns, with serial electrocardiograms beginning in infancy, might be expected to shed some light on this problem. Our limited observations on this point suggest that with atrial septal defects the electrocardiographic abnormalities are often well developed at an early age. Electrocardiograms taken at seven years of age or younger were available in six of our cases of persistent ostium secundum, and all showed a prominent RSR′-V1. In Case 8, for example, records taken at three years of age showed the same degree of right axis deviation and increased R′-V1 amplitude as were found at age seven. In Case 3 marked left axis deviation and an RSR′-V1 were already present at the age of twenty-two months. The intracardiac shunt and other functional consequences of the septal and valvular defects are also prominent at an early age, however, and it is impossi-

ble from such observations to determine whether the RSR′-V1 in these cases is itself a congenital anomaly or whether it is secondary to the strain imposed on the right ventricle.

Correlation between Electrocardiograms and Pressure-flow Measurements. Although the right ventricular hypertrophy which was present in these cases produced diagnostic electrocardiographic changes in twenty-two cases, these changes gave no quantitative information about the volume of the shunt or the degree of pulmonary hypertension. No useful correlation was found between the pulmonic to systemic flow ratio, the size of the defect, or the mean pulmonary artery pressure, and the mean QRS axis, V1 pattern, or height of R or R′ in V1. It is of interest, however, that the extremely tall R-V1 (2.0 millivolts or more) often seen with pulmonic stenosis was not observed in any of these cases of atrial septal defect.

First Degree A-V block. Prolonged PR intervals were present in six of our cases, confirming other observations[3] on the frequency of this disturbance with atrial septal defects. The incidence was particularly high in the cases of persistent ostium primum.

Arrhythmias. Wandering supraventricular pacemaker was present in two of the younger patients in this series; atrial fibrillation was found in three of the older patients. The remaining nineteen patients had a normal pacemaker, and abnormally high P waves occurred in six of these cases. Persistent sinus tachycardia was present in twelve cases.

Postoperative Changes. Surgical repair of the atrial defect was attempted in twenty-three cases. During the first postoperative week A-V nodal rhythm occurred in four patients, paroxysmal supraventricular tachycardia in one and rapid nodal tachycardia with varying degrees of A-V block in another. Complete heart block appeared in one patient after operation and persisted for three days.

Electrocardiograms have now been recorded six months or more after operation on nine patients. In seven cases right axis deviation has diminished or disappeared, with changes in mean QRS axis ranging from 15° to 70°. In one case which showed no change in axis, cardiac catheterization after operation revealed that the defect had not been completely closed. Electrocardiographic signs of right ventricular hypertrophy were still present in all nine cases from six months to two years after operation but in five cases the R′-V1 amplitude had decreased. In one patient (Case 11) left axis deviation and radiographic signs of left ventricular enlargement developed after operation, possibly due to mitral valve damage produced by one of the surgical sutures.

Differential Diagnosis of Atrial Septal Defects. It is not to be expected that the electrocardiogram will show pathognomonic features with atrial septal defects, or indeed in any disease, since the myocardial changes which are reflected in the electrocardiogram may be produced by a number of different structural abnormalities. Nevertheless there are some electrocardiographic findings which give at least a clue to the differentiation of atrial septal defects from other clinically similar lesions. For example, the combination of an apical diastolic murmur, systolic murmur in the pulmonic area, loud pulmonic second sound and enlarged pulmonary conus shadow may occur with severe mitral stenosis but if the electrocardiogram shows an RSR′-V1 and prolonged PR interval, an atrial septal defect is much more probable.

The signs of combined right and left ventricular hypertrophy in the electrocardiogram, which occur in cases of persistent ostium primum with mitral insufficiency, are comparatively rare with any other congenital lesion. They are sometimes found in ventricular septal defects but in such cases left axis deviation is usually absent.

It is essential, of course, not to overrate the importance of the electrocardiogram and to consider it in conjunction with all other diagnostic information available. The RSR′-V1 pattern, for example, is more common with atrial septal defect than with any other lesion but it also occurs often with pulmonic stenosis, chronic cor pulmonale, tetralogy of Fallot and other lesions with right ventricular enlargement, and sometimes with arteriosclerotic heart disease alone. Atrial fibrillation, to take another example, immediately brings to mind the possibility of mitral stenosis but it is also entirely compatible with atrial septal defect, especially in adults.

Anomalous pulmonary venous return, and Lutembacher's syndrome, give no characteristic electrocardiographic signs that we can discover. The electrocardiographic abnormalities found with these lesions do not differ from those in uncomplicated atrial septal defect. Cardiac catheterization may also fail to differentiate these anomalies, and surgical exploration is in many

cases the only way to make this differential diagnosis.

SUMMARY

1. In twenty-four patients with uncomplicated atrial septal defects, we have examined the electrocardiographic findings and their relation to the location and size of the defect, the degree of pulmonary hypertension and the ratio of pulmonic to systemic blood flow. The anatomic diagnosis was confirmed at autopsy in seven cases and at operation in seventeen cases. The septal defect was defined as persistent ostium primum in six cases and persistent ostium secundum in eighteen cases.

2. Electrocardiographic evidence of right ventricular hypertrophy was present in twenty-two cases. Right axis deviation appeared in eighteen cases.

3. Three patients had a persistent ostium primum, a cleft mitral leaflet and left as well as right ventricular hypertrophy, presumably due to mitral insufficiency. The electrocardiograms in these cases showed left axis deviation, with signs of both left and right ventricular hypertrophy.

4. One patient, aged fifty-two years, with a persistent ostium primum, normal mitral valve and autopsy evidence of coronary insufficiency due to atherosclerosis, showed left axis deviation and complete right bundle branch block.

5. An RSR′-V1 pattern was present in fifteen patients (63 per cent), two of whom had a QRS duration prolonged beyond 0.12 second. This confirms previous reports that this pattern occurs much more often with atrial septal defects than with other clinically similar lesions. The relatively high incidence of this pattern with any lesion which leads to right ventricular hypertrophy, however, and the lack of clear evidence as to its etiology suggest that it might be well to abandon the term "incomplete right bundle branch block" for the present.

6. Prolongation of the PR interval was present in four of six patients with persistent ostium primum, and two of eighteen patients with persistent ostium secundum.

CONCLUSIONS

1. Electrocardiographic signs of combined right and left ventricular hypertrophy with left axis deviation, in a patient with an atrial septal defect, suggest that the defect is a persistent ostium primum, with a cleft and insufficient mitral valve.

2. Cases of persistent ostium primum with no functional abnormality of the mitral valve cannot be distinguished electrocardiographically from cases of persistent ostium secundum. Both types produce electrocardiographic signs of right ventricular enlargement in almost all symptomatic cases. The RSR′-V1 pattern, and a prolonged PR interval, are present in a high proportion of cases.

ACKNOWLEDGMENTS

We are deeply indebted to the many persons whose help and cooperation were essential to this work, and wish particularly to express our thanks to: Dr. Henry Bahnson, Associate Professor of Surgery, Johns Hopkins University School of Medicine and Hospital, who operated on the majority of these patients, and to his staff in the Division of Surgical Physiology who carried out the cardiac catheterizations; Dr. Robert P. Grant and Dr. A. G. Morrow, of the National Heart Institute, for providing the information on Case 5; Dr. Helen Taussig, Associate Professor of Pediatrics, Johns Hopkins University School of Medicine, and Director, Harriet Lane Children's Cardiac Clinic, The Johns Hopkins Hospital, for permission to include cases from her clinic; Dr. Alexander S. Nadas, Associate Chief, Cardiology Division, Children's Medical Center, Boston, Massachusetts, for autopsy information on Case 1; Dr. R. W. Chesnut, Postdoctorate Research Fellow of the National Heart Institute, 1955–1956, for his assistance in the study of normal subjects; Mr. Arthur Briggs, fourth year student, The Johns Hopkins University School of Medicine, for his help with the general study of patients with right ventricular enlargement; and Miss Kate Fleenor, for her technical assistance in electrocardiography and vectorcardiography.

REFERENCES

1. Barber, J. M., Magidson, O. and Wood, P. Atrial septal defect with special reference to the electrocardiogram, the pulmonary artery pressure and the second heart sound. *Brit. Heart J.*, 12: 277, 1950.
2. Barker, J. M. and Valencia, F. The precordial electrocardiogram in incomplete right bundle branch block. *Am. Heart J.*, 38: 376, 1949.
3. Bedford, D. E., Papp, C. and Parkinson, J. Atrial septal defect. *Brit. Heart J.*, 3: 37, 1941.
4. Blount, S. G., McCord, M. C., Mueller, H. and Swan, H. Isolated valvular pulmonic stenosis. Clinical and physiologic response to open valvuloplasty. *Circulation*, 10: 161, 1954.

5. Braudo, J. L., Nadas, A. S., Rudolph, A. M. and Neuhauser, E. B. D. Atrial septal defects in children. *Pediatrics*, 14: 618, 1954.
6. Braunwald, E., Fishman, A. P. and Cournand, A. Time relationships of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. *Circulation Res.*, 4: 100, 1956.
7. Burrett, J. B. and White, P. D. Large interauricular septal defect with particular reference to diagnosis and longevity. *Am. J. M. Sc.*, 209: 355, 1945.
8. Carter, E., Richter, C. P. and Greene, C. H. A graphic application of the principle of the equilateral triangle for determining the direction of the electrical axis of the heart in the human electrocardiogram. *Bull. Johns Hopkins Hosp.*, 30: 162, 1919.
9. Edwards, J. E. Congenital malformations of the heart and great vessels. In: Gould, S. E. Pathology of the Heart. Springfield, Ill., 1953. Charles C Thomas.
10. Grishman, A. and Scherlis, L. Spatial Vectorcardiography. Philadelphia, 1952. W. B. Saunders Co.
11. McCulloch, H. Electrocardiographic studies of congenital heart disease. *Am. J. Dis. Child.*, 12: 30, 1916.
12. Milnor, W. R., Talbot, S. A. and Newman, E. V. A study of the relationship between unipolar leads and spatial vectorcardiograms, using the panoramic vectorcardiograph. *Circulation*, 7: 545 1953.
13. New York Heart Association. Nomenclature and Criteria for Diagnosis of Disease of the Heart and Blood Vessels. 5th ed. New York, 1953. Peter F. Mallon Co.
14. Rogers, H. M. and Edwards, J. E. Incomplete division of the atrioventricular canal with patent interatrial foramen primum (persistent common atrioventricular ostium). Report of 5 cases and review of the literature. *Am. Heart J.*, 36: 28, 1948.
15. Roesler, H. Interatrial septal defect. *Arch. Int. Med.*, 54: 339, 1934.
16. Sternberg, C. Beitrage zur Herzpathologie. (*a*) Umfangreicher Defekt im Septum atriorum mit Spaltung des Aortenzipfels der Mitralklappe. *Verhandl. d. deutsch path. Gesellsch.*, 16: 253, 1913.
17. Wilson, F. N., Rosenbaum, F. F. and Johnston, F. D. Interpretation of the ventricular complex of the electrocardiogram. *Advances Int. Med.*, 2: 1, 1947.
18. Ziegler, R. F. Electrocardiographic Studies in Normal Infants and Children. Springfield, Ill. 1951. Charles C Thomas.

Incomplete Transposition of the Great Vessels with Biventricular Origin of the Pulmonary Artery (Taussig-Bing Complex)*

Report of Four Cases and Review of the Literature

MICHELE A. CHIECHI, M.D.

Jersey City, New Jersey

THE Taussig-Bing complex[1] has aroused sufficient interest in the last few years to warrant an analysis of the reported cases and an assessment of this malformation among the transposition complexes.

"The malformation consists of a transposed aorta, a large pulmonary artery which arises primarily from the right ventricle and partially overrides the ventricular septum, a high ventricular septal defect, and right ventricular hypertrophy."[1] The Taussig-Bing heart is considered one of the rarest congenital cardiac anomalies. In Abbott's series of 1,000 cases of congenital heart disease there was no case of the Taussig-Bing type.[2] In the Centre de l'Hôpital Broussais' series of 1,100 cases of congenital heart malformations[3] there were only two cases, including the reported case of Metianu et al. In the recent book of Kjellberg and Coll[4] three cases of Taussig-Bing syndrome are listed in a series of 396 cases studied by the Swedish investigators. In none of these cases, however, was the diagnosis verified by autopsy.

Since the inception of the St. Michael's Hospital Department of Cardiac Surgery in 1950, the Taussig-Bing complex has been found in four cases in a series of seventy-two autopsies for congenital heart malformations. The over-all incidence of transposition of the great vessels was 25 per cent (eighteen cases including the four Taussig-Bing complexes). It would seem, therefore, that the anomaly is not as rare as the aforementioned statistics would lead one to believe.

CASE REPORTS

CASE I. This three and one-half month old white male infant, born after normal, spontaneous delivery, was noted to have generalized cyanosis at birth. The cyanosis was persistent and was made worse by crying, during feedings, and when the child was out of the oxygen tent. The respirations were labored, slightly irregular at times and rapid, at an average rate of 60 per minute. The heart rate at the apex was regular and averaged 164 per minute. Five days after birth a short, grade II systolic murmur was heard at the third intercostal space. Ten days after birth the child was given digitalis because of superimposed congestive heart failure. The color improved somewhat but the respirations remained labored and rapid up to the time of discharge at the age of four weeks. The child was maintained on digitalis. He did poorly at home and was brought back to the hospital three weeks later with the chief complaints of increased cyanosis and labored rapid breathing. On physical examination there was marked generalized cyanosis, more intense on the face and upper extremities than in the lower extremities. The heart rate was 120 and regular. There were no changes in the heart on physical examination. The respirations were regular, rapid, at a rate of 50 per minute, and labored with moderate inter- and subcostal retraction. Breath sounds were normal and no rales were detected. The liver edge was palpated one fingerbreadth below the costal margin. X-rays of the chest showed congestion and edema in both lung fields with secondary hilar enlargement. The heart silhouette was enlarged with suggestion of right ventricular dilatation. At fluoroscopy the radiologic findings were confirmed and the hilar vessels showed very active expansile pulsations. The electrocardiogram revealed sinus tachycardia, right axis deviation, a tall R wave in V_1, and T wave changes due to digitalis effect. The hematocrit was 57 per cent. The child was kept in an oxygen tent continuously. Digitalis was increased and mercurials were added in an endeavor to control the congestive failure. There was transitory improvement in the patient's color but the steady downhill course could not be checked in spite of all medications. The patient died

* From the Department of Cardiovascular Surgery, St. Michael's Hospital, Newark, New Jersey.

in congestive failure of the high output type three weeks after admission. The autopsy (Autopsy No. 2627) was limited to gross and histologic examination of the heart and lungs. The lungs showed marked congestion with pneumonic consolidation of the right upper lobe. The histologic examination of the heart showed only a moderate degree of congestion.

The heart was enlarged in all its diameters. It weighed 39 gm. (normal weight at this age, 27 gm.).[5] The heart measurements are summarized in Table 1. The apex was rounded and directed to the left. The anterior interventricular furrow appeared displaced to the right in its lower portion. The posterior interventricular sulcus ran down to the right of the posterior aspect of the heart.

The two auricles stood in normal relation to the four chambers and were not enlarged. The two atria were also in normal relation to the two ventricles. The upper anterior portion of the right ventricle showed a round prominence from which the aorta arose. The origin of the vessel was closer to the right than to the left border of the heart. Above its origin it proceeded upward and to the right, then to the left, forming an arch with its concavity to the left. (Fig. 1.) Immediately behind and to the left of the aorta was the much larger pulmonary artery, whose right margin was concealed by the ascending portion of the aorta. The huge, thick-walled pulmonary artery coursed vertically upward from the base of the heart for a distance of 2.3 cm., and then divided into the left and right pulmonary arteries which entered the left and right lung normally. (Fig. 2.) No winding about each other of the aorta and pulmonary artery occurred after their origin. The right side of the anterior surface of the ventricles was slightly prominent and was demarcated from the remainder by a shallow sulcus into which ran the anterior descending branch of the left coronary artery.

The right atrium was normal in size with well defined "crista terminalis" and "musculi pectinati" in the usual positions. The drainage of the venae cavae and coronary sinus was normal. There were normally formed valves at each opening. The foramen ovale was functionally closed but obliquely probe-patent on the interatrial wall with a semi-lunar valve coming from the posterosuperior aspect of it.

The right atrioventricular ostium, 5 cm. in length, was guarded by a normal tricuspid valve with normal posterior, anterior and medial leaflets. The cavity of the right ventricle was only slightly enlarged. The walls of the chamber were greatly hypertrophied, with a thickness varying from 0.5 to 1.5 cm. The inflow portion was inconspicuous. The outflow tract was moderately enlarged, with a markedly thickened wall on its superior aspect. Behind what seemed to represent the infundibulum of the right ventricle, an hypertrophied muscle band arched upward, laterally and slightly posteriorly from the upper third of the interventricular septum to the anterior wall of the right ventricle. (Fig. 3.) The medial portion of this arched muscular band was placed well apart from the ventricular wall, leaving therefore an adequate opening for the blood flow to the vessel arising from the summit of the infundibulum. The uppermost portion of the arch defined the posterior part of the base of the aorta. Its lateral portion appeared greatly hypertrophied for a length of 1.5 cm. In this part the band measured 1.1 cm. in width and constituted, with the anterior ventricular wall into which it merged, the thickest part of the right ventricular walls. This heavy muscular ledge acted as a false septum, 0.9 cm. deep, which divided the outflow tract of the right ventricle into a small anterior chamber and a large posterior portion. The band corresponded in position to the crista supraventricularis which, by assuming a more lateral course, had averted a narrowing of the infundibulum. No stenosis was therefore present in the path leading to the vessel arising from the infundibulum. Behind the crista and between it and the medial leaflet of the tricuspid valve was a deep recess which, at its apex, led to a defect of the interventricular septum and to the orifice of the pulmonary artery striding the defect. (Fig. 4.) The floor of this recess was almost entirely made up of a heavy muscular ridge. This ridge extended from the anterolateral wall of the ventricle, in close relation to the anterior papillary muscle, to the interventricular septum just behind the origin of the crista supraventricularis. It corresponded in location and function to the "trabecula septomarginalis" (moderator band) and gave insertion to chordae tendineae of the medial leaflet of the tricuspid valve. The aorta arose entirely from the chamber

TABLE 1
HEART MEASUREMENTS IN CASES I AND II

	Measurement (cm.)	
	Case I	Case II
Apex to base	5.2	4.9
Apex to summit of right atrium	5.9	5.7
Apex to summit of left atrium	4.6	5.2
Apex to atrioventricular groove (right margin)	5.2	6.0
Apex to atrioventricular groove (left margin)	3.9	3.9
Transverse diameter	5.1	6.2
Anteroposterior diameter	3.0	4.1
Right atrioventricular orifice (circumference)	5.0	4.0
Left atrioventricular orifice (circumference)	3.5	3.0
Aorta (circumference)	2.5	1.7
Pulmonary artery (circumference)	4.0	3.1

FIG. 1. Case I. The aorta, arising from the right ventricle, is anteriorly placed; behind is the greatly enlarged pulmonary artery. Both vessels course vertically upward, parallel to each other.

FIG. 2. Case I. The aorta has been displaced anteriorly and inferiorly to show the huge pulmonary artery.

FIG. 3. Case I. The aorta and the infundibulum of the right ventricle are opened. The white rod, advanced through the ventricular defect into the pulmonary artery, exteriorizes the crista supraventricularis (arrow), bringing it into view. The defect, located behind the crista, is hidden by the crista.

limited anteriorly by the right anterior ventricular wall and posteriorly by the crista supraventricularis. It measured 2.5 cm. in circumference and had three well formed semi-lunar cusps with three normal sinuses. The coronary-bearing cusps were the left anterior and the posterior. The non-coronary cusp was the right anterior (B. N. A. system).

The left atrium was greatly dilated and displaced posteriorly. It drained four considerably enlarged pulmonary veins. Its walls were thicker than those of the right atrium.

The left atrioventricular ostium was normal in appearance, measuring 3.5 cm. in circumference, and was guarded by a normal mitral valve. The two major leaflets, the corresponding chordae tendineae and papillary muscles presented no abnormalities. The cavity of the left ventricle was moderately enlarged, particularly in its outflow portion. The wall thickness ranged from 0.2 to 0.7 cm.

The interventricular septum was thicker in its lower portion but became thinner above to present a semicircular defect in its upper section. The defect (Fig. 5), measuring 1.2 by 0.6 cm., replaced entirely the "pars membranacea septi" and permitted introduction of the tip of the index finger. The anterior, inferior and part of the posterior margins of the defect consisted of septal muscle. The attachment of the medial leaflet of the tricuspid valve constituted the remaining portion of the posterior margin. The superior margin, really located in the cavity of the right ventricle, was formed anteriorly by the right posterior semi-lunar cusp of the pulmonary artery and posteriorly by the annulus fibrosus of the pulmonary artery. By means of this defect the left ventricle communicated freely with the right ventricle. Above the defect and at the summit of the outflow tract of the left ventricle was the base of the pulmonary artery which measured 4 cm. in circumference. It was a large, thick-walled vessel with three semi-lunar cusps, one anterior and two posterior. It straddled the interventricular communication. The left anterior margin of this vessel continued down to the anterior leaflet of the mitral valve. The right posterior margin was in relation with the medial leaflet of the tricuspid valve. By producing closure and bulging of the semi-lunar cusps, the degree of overriding of the pulmonary artery was anatomically estimated to be one-third of its base.

The aorta gave off the right subclavian artery at a distance of 2.3 cm. from its origin and from the posterior aspect of the arch. At approximately the same level was seen a common carotid trunk arising from the anterior aspect of the arch. The origin of the left subclavian artery occurred at the end of the arch proximal to a closed ductus arteriosus. Distal to the ductus was an area of coarctation which reduced the aortic lumen to one-fourth of its original size. The coarctation consisted of a smooth crescentic diaphragm with an eccentric opening, placed on the posteromedial wall of the aorta.

FIG. 4. Case I. Two white rods emerge from the pulmonary trunk. One is passed from the right ventricle through the interventricular communication; the other runs over the outflow tract of the left ventricle. The slender marker runs through the infundibulum of the right ventricle into the aorta.

The left coronary artery originated from a very large orifice in the left anterior aortic sinus. It immediately divided into the left circumflex and anterior descending branches. The further course and distribution of the vessel exhibited the usual essential characteristics of the left coronary artery. The right coronary artery arose in the posterior aortic sinus very close to the junction of the posterior with the right anterior cusp. The vessel emerged between the aorta and the right atrium and formed the right circumflex artery with its terminal portion as the posterior descending artery. The distribution of this vessel was typical of the right coronary artery. (Fig. 6.) We are dealing with a complete transposition of the blood supply of the heart caused by an exchange in position of the sinuses of Valsalva. By virtue of a high degree of counterclockwise rotation, the right sinus of Valsalva is rotated to the left and the left sinus posteriorly and slightly to the right. All the branches of the right coronary artery arise from the original left coronary orifice.

The anatomopathologic diagnosis was: marked cardiac hypertrophy, functionally closed foramen ovale, large interventricular septal defect, incomplete transposition of the great vessels, large and overriding pulmonary artery (Taussig-Bing heart), rotation of coronary arteries orifices, complete transposition of the coronary arteries and coarctation of the aorta.

FIG. 5. Case I. The large interventricular septal defect, straddled by the pulmonary root, is viewed from the left ventricle. The posterior aspect of the crista supraventricularis in the right ventricular cavity can be seen below the pulmonary valve.

CASE II. This ten week old white male infant had a normal delivery and at birth was allegedly not cyanotic. An evaluation of his cardiac status was made when the child was admitted to the hospital because of failure to gain weight. Physical examination disclosed a poorly developed and undernourished, mildly cyanotic child, resting quietly with no venous distention. Positive clinical findings were limited to the lungs, heart and liver. There were moist respiratory rales at the left lung base. A systolic murmur heard best at the base of the heart and left sternal border was present. The liver was palpable one finger-breadth below the right costal margin. The heart rate was rapid, 180, but regular, and the femoral pulses were faintly palpable. On fluoroscopy the heart was enlarged in its transverse diameter with prominence of the anterior border in both obliques. Hilar vessels were very prominent. X-rays of the chest confirmed the fluoroscopic findings. The electrocardiogram showed sinus tachycardia, right axis deviation and right ventricular hypertrophy. The hospital course was one of relentless worsening of the cardiac status with increasing cyanosis and dyspnea. The respirations increased to 80 per minute. The liver was markedly enlarged and peripheral edema was present. Digitalis and mercurials were of no help and the patient died in pulmonary edema two weeks after admission. The autopsy (Autopsy No. 1828) was limited to gross and histologic examination of the heart and lungs. The lungs showed edema and hemorrhagic congestion.

Microscopic examination of the heart disclosed no unusual findings.

The heart was markedly enlarged in all its diameters and was almost triangular in appearance because an unusual prominence was present on the upper portion of the right heart margin. The organ weighed

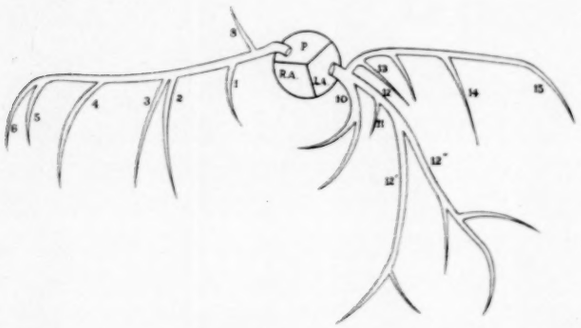


FIG. 6. Coronary circulation in Case 1. Right coronary artery: (1) arteria adiposa dextra, (2) ramus ventriculi dextri anterior, (3) ramus margini acuti, (4) ramus ventriculi dextri posterior, (5) ramus sulci longitudinalis posterioris, (6) ramus ventriculi sinistri posterior, (8) ramus atrialis dexter anterior. Left coronary artery: (10) arteria adiposa sinistra, (11) arteria septi ventriculorum, (12) ramus collateralis descendens anterior, (12′) ramus primus, (12″) ramus secundus, (14) ramus margini obtusi, (15) ramus ventriculi sinistri posterior.

42.5 gm. (normal weight at this age 23 gm.).[5] The heart measurements are summarized in Table 1. The region of the apex was uniformly rounded and there was no definite apex. The long axis of the heart was directed downward and to the left. The anterior interventricular groove appeared displaced to the left, while the posterior groove ran down in the middle of the posterior aspect of the heart.

The heart appeared rotated to the right so that the right auricle was placed posteriorly and the left auricle more anteriorly. The auricles, however, stood in normal relation to the four chambers and were not enlarged. The two atria were also in normal relation to the two ventricles. The upper anterior aspect of the heart showed a round prominence from which the aorta arose. This prominence was placed at about the middle of the base of the heart. From its origin the aorta coursed vertically upward and to the left. The pulmonary artery was enlarged and situated posteriorly. It ran directly upward (Fig. 7) for a distance of 1.7 cm. and then divided into two main branches, left and right, which entered the left and right lung normally. There was no evidence of twisting of the aorta and pulmonary artery about each other after their origin.

The size of the right atrium was larger than normal. The fossa ovalis was well formed and the foramen ovale, 0.15 cm. in diameter, was patent. The wall of the atrium was 0.1 cm. thick and heavily trabeculated.

The right atrioventricular orifice measured 4 cm. in circumference and bore an anterior, a medial and a small posterior cusp. The cavity of the right ventricle was enlarged and its walls were greatly hypertrophied. The thickness of the walls varied from 0.3 to 1.3 cm. over the aforementioned prominence on the right heart margin. The sinus or inflow portion of the ventricle was not striking. The anterior papillary muscle was normal while the posterior was smaller than normal. The medial cusp was bound by chordae partly to the posterior papillary muscle and partly to the septum. The outflow tract was slightly enlarged with a moderately thickened wall. This part of the right ventricle gave rise to the aorta at its summit. A moderately heavy muscular ledge, 0.5 cm. deep, ran from the anterior wall of the ventricle in close relation to the anterior papillary muscle to the lower third of the interventricular septum. Almost in continuation of this ledge, a thick rounded ridge arched across the roof of the right ventricle from the interventricular septum. (Fig. 8.) It ran upward, backward and laterally behind the aortic orifice and in front of the anterior leaflet of the tricuspid valve to reach and merge into the anterolateral wall of the ventricle, at a considerable distance from the anterior papillary muscle. The first muscular ledge corresponded in position to the trabecula septomarginalis and the latter to the crista supraventricularis. Together, these two ridges circumscribed an irregularly rounded wide aperture between the larger posterior (inflow tract) and the smaller anterior portion (outflow tract) of the right ventricle. Behind the crista and between it and the medial tricuspid leaflet was a large recess whose summit led to a defect of the interventricular septum and to the origin of the pulmonary artery, which straddled the defect. The defect was oval in shape and measured 0.9 by 0.5 cm. On the right it appeared to be limited anteriorly by the posterior margin of the arched portion of the crista, superiorly by the anterior and right posterior cusps of the pulmonary artery, posteriorly by the insertion of a portion of the medial tricuspid leaflet and inferiorly by the superior margin of the ventricular septum.

The aorta arose from the summit of the infundibulum, the walls of which were formed anteriorly by the anterior wall of the right ventricle and posteriorly by the crista. The direction of the crista in its arched portion was such that no stenosis resulted at the level of the infundibulum. The crista acted like a pseudoseptum between the aortic and pulmonary openings. The aorta measured 1.7 cm. in circumference and was guarded by three normally formed semi-lunar cusps with three normal sinuses. The coronary cusps were represented by the posterior and left anterior (B. N. A. system).

The left atrium was dilated and received the venous drainage of the lungs. Its walls were as thick as those of the right atrium.

The left atrioventricular orifice appeared normal, measured 3 cm. in circumference and bore a normal

mitral valve. The left ventricular chamber appeared enlarged particularly in its outflow portion. The thickness of the wall varied from 0.3 to 0.6 cm. The septal defect was situated in the superior portion of the septum. Viewed from the left, the defect was limited inferiorly and anteriorly by the muscular edge of the septum, posteriorly by the attachment of a portion of the medial tricuspid leaflet and superiorly by the undersurface of the anterior and right posterior pulmonary cusps. The superior margin was not a margin in a true sense, because of the overriding of the pulmonary trunk; the anterior and right posterior pulmonary cusps were partially displaced into the right ventricular cavity. At the summit of the outflow section of the left ventricle and sitting well astride of the interventricular septal leaflet was the orifice of the pulmonary artery. (Fig. 9.) It was a large, thick-walled vessel, measuring 3.1 cm. in circumference and guarded by three normally formed semi-lunar cusps, one anterior and two posterior. The left anterior portion of the pulmonary base extended down to the anterior mitral leaflet. The degree of overriding of the pulmonary artery was anatomically estimated to be about 35 per cent of the orifice.

The aorta gave off its first branch at a distance of 2 cm. from its origin. The left carotid and subclavian arteries were given off in succession, considerably reducing the lumen of the aorta. The length of the hypoplastic aorta was about 1 cm. The ductus arteriosus opened distally to this segment. Its lumen was probe-patent.

The orifice of the left coronary artery was of normal size and located anteriorly in the left aortic sinus. The vessel immediately trifurcated into left circumflex, accessory descending and anterior descending branches. The right coronary artery originated from a large orifice rather anteriorly placed in the posterior aortic sinus. The artery, coursing between the aorta and the right atrium, continued in the right atrioventricular groove. It gave off the usual branches to the right ventricle, and terminated in an important branch to the posterior aspect of the heart. (Fig. 10.)

The anatomopathologic diagnosis was: marked cardiac hypertrophy, minute foramen ovale, large interventricular septal defect, incomplete transposition of great vessels, large and overriding pulmonary artery (Taussig-Bing complex), rotation of coronary artery orifices, complete transposition of coronary arteries, hypoplasia of the aorta and patent ductus arteriosus.

CASE III. This two month old white male infant was referred to the hospital because of continuous rapid respirations and cyanosis. The child had a normal, spontaneous delivery, and was noted to have a "dusky color" associated with gasping cough four days after birth. At the age of six weeks rapid, labored breathing and vomiting spells developed in the patient, which resulted in his admission.

FIG. 7. Case II. The heart and both lungs are viewed from above. The aorta arises anteriorly and the pulmonary artery, greatly enlarged, is immediately behind it. No winding of the two vessels about each other occurs.

FIG. 8. Case II. The aorta and infundibulum of the right ventricle are opened. The white rod runs into the pulmonary artery through the ventricular defect. The crista supraventricularis, smaller than that in Case I, is clearly in view.

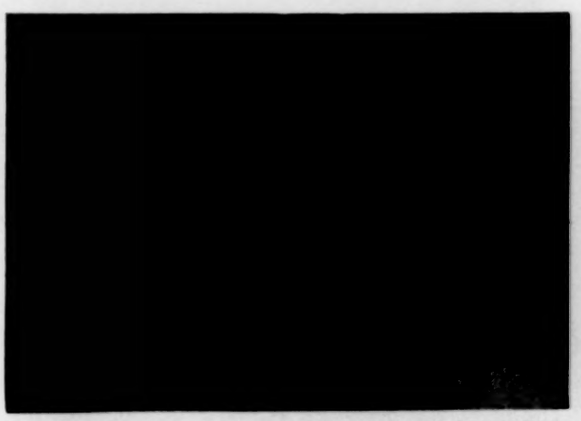


FIG. 9. Case II. The pulmonary artery overriding a large interventricular communication is viewed from the left ventricle.

On physical examination the child was cyanotic and in marked respiratory distress. Respirations were 80 per minute. The heart rate was rapid, 180, but regular, and the femoral pulse was faintly palpable. Systolic blood pressure was 110 in the upper and 76 in the lower extremities, indicating coarctation of the

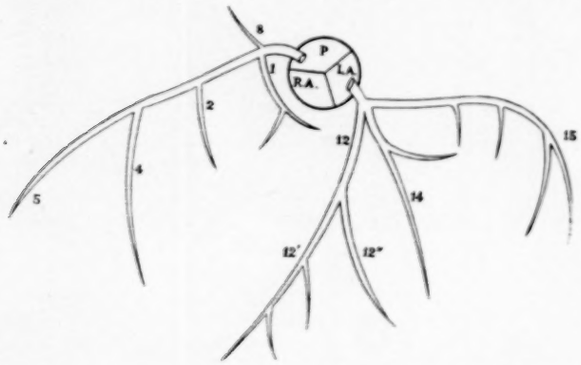


FIG. 10. Case II. Coronary circulation in Case II. Right coronary artery: (1) arteria adiposa dextra, (2) ramus ventriculi dextri anterior, (4) ramus ventriculi dextri posterior, (5) ramus sulci longitudinalis posterioris, (8) ramus atrialis dexter anterior. Left coronary artery: (12) ramus collateralis descendens anterior, (12′) ramus primus, (12″) ramus secundus, (14) ramus margini obtusi, (15) ramus ventriculi sinistri posterior.

aorta. There was a systolic murmur over the precordium, best heard at the second and third intercostal spaces to the left of the sternum. The pulmonary second sound was equal in intensity to the aortic second sound. The lungs were clear and the liver was palpated three fingerbreadths below the costal margin. There was cyanosis of the nail beds but no clubbing. On fluoroscopy the heart was enlarged particularly on the right where the right atrium appeared greatly dilated. The aorta was dextroposed and the vascular markings were markedly accentuated. X-rays of the chest confirmed the findings at fluoroscopy. The electrocardiogram indicated sinus tachycardia, right axis deviation and right ventricular strain. Red blood cells were 4.8 million per cu. mm., hemoglobin 14 gm. per cent and the hematocrit 48 per cent.

The patient was kept in an oxygen tent constantly and given digitalis and mercurials, with no improvement. There was progressive deterioration. The heart rate and respirations remained rapid and the cyanosis deepened. Severe pneumonia on the right side preceded death, which followed an episode of pulmonary edema, one month after admission.

At autopsy (Autopsy No. 2349) findings were: massive pneumonic consolidation and multiple hemorrhages of the lungs, visceral congestion and hydrocele. The heart was described as markedly enlarged, displacing both lungs. It weighed 45 gm. (normal weight at this age 23 gm.).[5] The two auricles were slightly dilated. The right and left atrium normally drained the systemic and pulmonary veins, respectively, and were in normal relationship to both ventricles. The foramen ovale was sealed. The tricuspid and mitral valves were normal and competent. Both ventricles were markedly dilated and hypertrophied. The aorta arose from the right ventricle. The pulmonary artery originated mainly from the left ventricle and in part from the right ventricle. Its base straddled a large high interventricular septal defect. The coronary arteries arose from the posterior sinuses of Valsalva. The ductus arteriosus was closed and there was coarctation of the aorta.

CASE IV. This twenty-one month old Negro female child was admitted because of increasing dyspnea and cyanosis, dry cough, syncope, anorexia, vomiting and failure to gain weight. The patient was delivered with the aid of forceps and was cyanotic at birth. The child was seen for the first time in our clinic at the age of three weeks. At that time, very rapid breathing, and cyanosis of fingernails and toenails were noted. On examination of the heart a systolic murmur was heard over the precordium, most intense at the fourth intercostal space to the left of the sternum. Red blood cells were 5.1 million per cu. mm. and hemoglobin 14.5 gm. per cent. No noticeable changes were observed at a later check-up when the patient was six months old. Upon admission to the hospital the child was found to be in congestive heart failure. The heart rate was 134, respirations were rapid and labored. The liver was palpable four fingerbreadths below the costal margin. Fluoroscopy revealed marked dilatation of all the chambers of the heart. Both lung fields appeared congested with prominent non-pulsating hilar vessels. X-rays of the chest confirmed the fluoroscopic findings. The electrocardiogram indicated right atrial and right ventricular hypertrophy. The blood picture was peculiar for a cyanotic child in that the red blood cell count was 4 million per cu. mm. with a hemoglobin of 7.5 gm. per cent. Peripheral blood smears showed severe achromia, poikilocytosis, anisocytosis, many target cells and occasional macrocytes. The findings were interpreted as those of an iron-deficiency anemia. The child was placed in an oxygen tent and was given digitalis, mercurials and low salt diet, small transfusions and iron preparations. The blood picture improved markedly (red blood cells 5.9 million per cu. mm., hemoglobin 14.5 gm. per cent). The cardiac failure persisted in spite of all medications and the child died in pulmonary edema ten weeks after admission.

At autopsy (Autopsy No. 2227) the pertinent findings were: congestion, edema and patchy hemorrhages of both lungs, severe visceral congestion with multiple small hemorrhages. The heart was markedly enlarged and oval shaped. The pericardial sac contained a considerable amount of straw-colored fluid. Both atria were markedly dilated and were in normal relationship to the ventricle. The foramen ovale was

completely sealed. The right ventricle was greatly hypertrophied but the lumen did not appear to be dilated. The tricuspid and mitral valves were normal in appearance and without vegetations. The aorta arose from the right ventricle and was slightly smaller in caliber than normal. There was a high, large interventricular septal defect. A markedly dilated pulmonary artery originated from the right and left ventricle, and its base straddled the ventricular communication. The left ventricle was greatly dilated with no apparent hypertrophy of the wall. There was a single coronary artery orifice situated in the posterior sinus of the aorta. The vessel divided into right and left branches. There was a patent ductus arteriosus of considerable size.

REVIEW OF THE LITERATURE

The reported cases of the Taussig-Bing complex are few. (Table II.) The number of cases with documented evidence of the fundamental criteria for the pathologic diagnosis of this anomaly is even smaller.

Pernkopf in 1933, in collaboration with Wirtinger,[6] proposed a theory of the cause of transposition. In an earlier report[7] he anticipated this type of malformation, on embryologic grounds, tabulating it among the partial transpositions.

Brown[8,9] states that in cases of transposition with interventricular septal defect "the pulmonary artery situated posteriorly, may override the defect and thus arise from both ventricles." In writing about the radiologic findings in transposition of great vessels, he further discusses overriding of the pulmonary artery.

In 1949 Taussig and Bing[1] reported their well documented case and discussed the physiologic and clinical implications of the syndrome. Their patient, a five and one-half year old, poorly developed girl, cyanotic since birth and dyspneic at rest, was thought clinically to have an Eisenmenger complex. Physiologic study, however, indicated a transposition of the great vessels. After angiocardiographic examination the patient died suddenly and the autopsy revealed the peculiar type of transposition.

The pathologic anatomy of the Taussig-Bing complex was carefully described a year later by Lev and Volk.[10] The patient was one year old and was known to have congenital heart disease from birth. No other details were available. The child was brought to the hospital because of an upper respiratory infection and died a day later with the clinical picture of congestive heart failure. We shall have occasion to discuss later the anatomic findings of this case.

In the same year a group of Swedish investigators[11] reported two cases of "Transposition of the Aorta." In the first case a diagnosis of transposition of great vessels with pulmonary artery overriding an interventricular septal defect was made on the basis of physiologic studies. The low pressure in the pulmonary trunk, the absence of hilar pulsations and other physiologic considerations suggested an inadequate pulmonary circulation. Consequently a Blalock procedure was advised; the surgery could not be completed for anatomic reasons and the patient died a few days after operation. The autopsy revealed a Taussig-Bing heart and, in addition, a patent foramen ovale with no pulmonary stenosis. The low pulmonary artery pressure and the absence of hilar pulsations were thought to be due to a "functional pulmonic stenosis." In the second case conclusive evidence of the presence of a Taussig-Bing complex is not afforded by the findings given by the authors. This case will not be considered in this report.

In 1951 Bayer[12] gave an account of a patient who is the oldest living subject with Taussig-Bing syndrome reported to date. The observation deals with a twenty-four year old, underdeveloped and physically disabled man, who was cyanotic from birth. The patient was always short of breath and two years before admission had an episode of hemoptysis. There was marked cyanosis and clubbing of fingers and toes. A systolic murmur was heard at the base of the heart. Radiographic examination showed an enlarged heart with a very prominent pulmonary conus. The hilar shadows were increased and hyperpulsatile. There was slight right axis deviation on the electrocardiogram. Catheterization of the heart revealed a higher oxygen saturation in the pulmonary artery than in the aorta. This finding, together with the history, prompted the diagnosis of Taussig-Bing anomaly.

In 1952 Martin and Lewis[13] reported a case of Taussig-Bing syndrome in a nine year old patient. The clinical diagnosis was established by the observations of a higher oxygen saturation of the pulmonary artery blood than of the aortic blood, and an angiocardiogram showing simultaneous filling of the aorta and pulmonary artery from the right ventricle one and one-half seconds after injection of the dye. There was no autopsy to verify the diagnosis of Taussig-Bing anomaly in this case.

Metianu et al.[3] in 1953 reported a Taussig-Bing syndrome in a six year old patient. The

TABLE II

COMPARATIVE CLINICAL AND PHYSIOLOGIC FEATURES OF THE REPORTED CASES OF TAUSSIG-BING COMPLEX

Author, Year	Age and Sex	Development	Cyanosis	Dyspnea	Clubbing	Murmurs	Electrocardiography	Red Blood Cells (million per cu. mm.)	Hemoglobin (gm. %)	Hematocrit (%)	Fluoroscopy	X-ray	Catheterization Findings
Taussig and Bing, 1949	5 yr., F	Underdeveloped	Marked since birth	Marked; squatted at 3 yr., no squatting thereafter	Marked	Systolic	Right axis deviation, right ventricular hypertrophy	9.3	23.5	77 *	Fullness of pulmonary conus; increased hilar shadows, faintly pulsating	Slightly enlarged heart; angiogram: aorta promptly visualized, little dye in pulmonary artery	Higher O_2 saturation in pulmonary artery than in aorta; fall of O_2 saturation with exercise
Lev and Volk, 1950	1 yr., M	Cyanotic from birth, details unknown	Present	Present	.....	To-and-fro murmur over precordium	.....	...	.....	....	.....	Enlarged heart	.....
Van Buchem et al., 1950 1s case	12 yr., F	Slight build	Marked since birth	.....	Marked	Loud, rough systolic over precordium	Right axis deviation, right ventr. hypertrophy	6	16*	.....	Increased hilar markings, no pulsations	Slightly enlarged heart; angiogram: prompt opacification of aorta from right ventricle	Higher O_2 saturation in pulmonary artery than in aorta; catheter in pulmonary artery from right ventricle; low pressure in pulmonary artery
Bayer, 1951	24 yr., M	Underdeveloped	Marked since birth	Moderate	Marked	Systolic at base	Right axis deviation	7.7	19.5*	80	Hilar shadows increased with pulsations	Enlarged heart; markedly prominent pulmonary conus	Higher O_2 saturation in pulmonary artery than in aorta
Martin and Lewis, 1952	9 yr., M	Underdeveloped	Moderate since birth	Fair exercise tolerance; squatted after exercise	Moderate	Grade II systolic, booming P_2	Right ventr. hypertrophy, right bundle branch block incomplete	.....	.....	.....	Expansile pulsations of markedly increased hilar markings	Enlarged heart; angiogram: simultaneous opacification of aorta and pulmonary artery	Higher O_2 saturation in pulmonary artery than in aorta
Metianu et al., 1953	6 yr., F	Underdeveloped	Moderate since birth	Marked	Moderate	Systolic thrill, loud, rough systolic, loud P_2	Right axis deviation, right ventricular hypertrophy	4.5	11.8*	....	Increased and hyperpulsatile hilar markings	Enlarged heart; markedly prominent pulmonary conus	Pulmonary artery entered from right ventricle; no O_2 determination
Maxwell and Crumpton, 1954, 1st case	4 mo., F	Underdeveloped, mongolian	Moderate since birth	.....	.....	Systolic thrill, Grade III-IV systolic murmur	Right axis deviation	....	.....	....	Fullness of pulmonary conus; hypervascularity of lung fields; no pulsations	Enlarged heart; angiogram: prompt visualization of aorta from right ventricle	.....
Espino Vela, 1955	10 yr., F	Underdeveloped	Moderate beginning at 3 yr.	.....	Moderate	Rough systolic, loud P_2	Combined ventricular hypertrophy	5.7	18	52	Markedly prominent and pulsating pulmonary artery and hilar vessels	Enlarged heart; markedly increased hilar shadows	Higher, but variable, O_2 saturation in pulmonary artery than in aorta; fall of O_2 saturation with exercise
Author, Case I	3½ mo., M	Underdeveloped, 7 lbs.	Marked since birth	Marked at rest	.....	Grade II systolic	Right axis deviation	5.9	17	57	Markedly increased vascular markings, pulsating hilar vessels	Enlarged heart	.....
Author, Case II	10 wk., M	Underdeveloped, 6.5 lbs	Moderate, no cyanosis at birth?	Marked	.....	Systolic over precordium	Right axis deviation, right ventricular hypertrophy	4.8	11.8	....	Very prominent, nonpulsating, hilar vessels; extensive pulmonary congestion	Markedly enlarged heart	.....
Author, Case III	2 mo., M	Underdeveloped, 8 lbs.	"Dusky color" 4 days after birth; marked cyanosis at 1 mo.	Marked	.. ..	Systolic over precordium	Right axis deviation, right ventricular strain	4.8	14	48	Markedly accentuated vascular markings; no pulsations	Markedly enlarged heart	.....
Author, Case IV	21 mo., F	Underdeveloped, 20 lbs.	Marked at birth	Marked	.....	Systolic to left of sternum, 4th ICS	Right atrial and right ventricular hypertrophy	4	7.5	31.5	Congested lung fields with engorged but nonpulsating vessels	Marked dilatation of all the chambers	.....

* The percentage values given by the authors have been converted using the Sahli hemoglobinometer.

clinical diagnosis was that of "vascular transposition, probably Taussig-Bing syndrome." The patient had been cyanotic since birth and had moderate clubbing of fingers and toes. On catheterization the pulmonary artery was entered from the right ventricle and a systolic pressure of 92 to 96 was recorded. The patient died of unexplained coma three days after the catheterization of the heart. At autopsy there was a Taussig-Bing heart with hypoplasia of the aorta and a fetal type of circulation through a patent ductus arteriosus. One interesting feature of the anatomy of this patient was that the infundibulum of the right ventricle was slightly posterior to the pulmonary artery but anterior to the tricuspid valve.

In 1954 Maxwell and Crumpton[14] reported two cases of the Taussig-Bing heart. The first subject, a four month old mongolian female, was noted to have a cyanotic right hand since birth. Following paroxysms of cough at two months of age, the cyanosis became more widespread and constant. At four months there was cyanosis over the brows, cheeks and lips at rest. Death occurred at six months following a severe respiratory infection. The autopsy established the diagnosis of Taussig-Bing complex. There was also a coarctation of the aorta with a fetal type of circulation through a patent ductus arteriosus. In the authors' second case the diagnosis of Taussig-Bing syndrome can be assumed only on observations which are far from critical in establishing the diagnosis of the anomaly under discussion. This case will not be considered in this paper.

Three cases of Taussig-Bing complex were reported by Kjellberg and Coll.[4] In one case the patient was a twenty month old boy with cyanotic episodes since the age of one month. The diagnosis was established by means of angiocardiography, which clearly showed a biventricular pulmonary artery. In this case the distal part of the aortic arch was hypoplastic and there was a patent ductus arteriosus distal to it. In the other two cases the clinical and laboratory findings were not sufficient to confirm a diagnosis of Taussig-Bing complex. These last two cases will not be considered in this report.

Moragues and Lynxwiler[16] reported three cases, two with pictures of the heart specimens. Of these two, one is a true Taussig-Bing heart while the other is a case of corrected transposition of the aorta with the pulmonary trunk above the defect but not clearly overriding it. The last case and the third, which is documented only by two radiograms, will not be discussed because no other details are given.

The last published case of Taussig-Bing complex is that of Espino Vela[15] which appeared in 1955. This ten year old poorly developed girl had cyanosis and clubbing of fingers since the age of three years, associated with limited exercise tolerance. There was a rough systolic murmur and a loud pulmonary second sound. The electrocardiogram suggested combined ventricular hypertrophy. A diagnosis of Taussig-Bing complex was made on the basis of x-ray and catheterization findings. There was marked prominence of the pulmonary artery region with hyperpulsatile hilar shadows at fluoroscopy. The catheterization findings were indicative of a transposition of great vessels, including a fall in oxygen saturation of the arterial blood after exercise.

Comment. The anatomic description of the cases in which the diagnosis was verified at autopsy is generally inadequate. Anatomic evaluation of the degree of overriding is usually difficult and the various authors make no effort to determine it. No account is given of the anatomic features of the right ventricular cavity which with other criteria, are essential for establishing the diagnosis in any type of transposition.[17] No mention is made of the coronary ostia and of the distribution of the coronary arteries and a case is reported in which the authors state that the coronary circulation was normal. If we were to accept in this review only the cases acceptably meeting the criteria for the anatomic diagnosis of transposition, we would have to eliminate the majority of the reported cases of Taussig-Bing heart.

Of the ten cases verified by autopsy, including our four, an abnormality of the aorta was found in five cases. In three cases there was a coarctation of the aorta of the so-called "adult type" (two of our cases and the case of Maxwell and Crumpton). In our two patients the ductus arteriosus, located proximal to the coarctation, was sealed. In Maxwell and Crumpton's patient the coarctation was located between the left carotid and the left subclavian artery, and was proximal to a patent ductus arteriosus that seemed to permit flow into the descending aorta. In the case of Metianu et al. and in another of our cases hypoplasia of the aorta distal to the left subclavian artery was present. The ductus arteriosus opened distally to the stenosis and it

was only probe-patent in our patient, while it was widely patent in Metianu's patient with a fetal type of circulation.

The high incidence of abnormalities of the aortic arch system found in the Taussig-Bing complex (50 per cent of the autopsied cases) is unexplained.

The cases in which the diagnosis was established on clinical, physiologic and angiocardiographic grounds seem questionable. At times, the diagnosis has been made only on assumptions (second case of van Buchem et al.) and often on the basis of angiocardiographic findings, which do not show conclusively the main feature of the Taussig-Bing syndrome, that is, the biventricular origin of the pulmonary artery. The same objection can be made to the diagnostic conclusion drawn from catheterization studies. We do not agree with the opinion that the passage of a catheter from the right side of the heart into the aorta and the pulmonary trunk or finding the oxygen saturation of the blood in the pulmonary artery greater than that in the aorta or peripheral arteries are critical in establishing the presence of a Taussig-Bing complex.[18] The position of the aorta and pulmonary artery can be easily established by fluoroscopy during cardiac catheterization if the catheter passes into both vessels. However, in addition to the fact that this can happen in any given case of transposition with an interventricular septal defect, the finding gives no clue as to the relation of the vessels to the ventricular septum. The latter relationship, the overriding of the pulmonary artery, is essential for the diagnosis of the Taussig-Bing anomaly. The presence of a much higher oxygen saturation in the pulmonary artery than in the aorta is likewise not diagnostic since it is a feature common to cases of complete and functional transposition. Furthermore, "the evaluation of shunts by means of gas analysis is uncertain in cases of transposition,"[19] because of the variation of the shunts from moment to moment.

The diagnosis of Taussig-Bing complex is certainly enticing in the case of Bayer. The findings, however, are not different from those of a complete transposition with a large interventricular communication. With due consideration given to the history, the x-ray picture with a very prominent pulmonary conus can be considered almost typical of the anomaly, as we shall see later in the discussion.

The case of Espino Vela is suggestive of a Taussig-Bing syndrome but the absence of cyanosis in the first three years of life is strongly against it. Our experience and that of authors who have written on transposition of great vessels,[4,9,19,20,26,27,29,30] of which the Taussig-Bing anomaly is one of the variants, show that cyanosis from birth or shortly thereafter is an obligatory sign of the malformation and is the "logical outcome of the anatomical abnormality."[9]

Angiocardiography can be diagnostic in cases in which the dye clearly outlines the septum and the overriding of the pulmonary artery. Simultaneous visualization of the aorta and pulmonary artery is certainly not pathognomonic since this happens in cases of complete transposition with a large interventricular communication. Outlining of the ventricular septum with a clear display of the biventricular origin of the pulmonary artery is the essential requisite for making the diagnosis of incomplete transposition with overriding pulmonary artery. Of the published angiograms this most important feature could be assessed with certainty only in the first case of Kjellberg et al. (*loc. cit.*: Fig. 473) and perhaps in the angiogram reported by Keith.[21] Simultaneous opacification of the right ventricle and aorta as well as the left ventricle and pulmonary artery (case of Maxwell and Crumpton) is seen in complete transposition with a large ventricular defect. The septum is clearly visualized in the case of Martin and Lewis but there seems to be no biventricular origin of the opacified pulmonary artery; the left margin of the pulmonary root is in line with the left margin of the septum and there is no appreciable overriding. In the case of Maxwell and Crumpton "the pulmonary artery is in close relationship to the ventricular septal defect," but certainly not overriding the defect.

The foregoing discussion emphasizes the difficulty of establishing the diagnosis of the anomaly *in vivo*. The clinical features and, in some respects, the other complementary studies are almost identical to those occurring in complete transposition with interventricular communication. Only angiocardiographic visualization of the biventricular origin of the pulmonary artery establishes indisputably the diagnosis between a complete and an incomplete transposition of the Taussig-Bing type.

COMMENTS

The Taussig-Bing complex belongs to the group of incomplete transposition of the great

vessels. The basic anomaly is the abnormal position of the arterial trunks, a defect of the interventricular septum and the relationship of the pulmonary artery to the septal communication. We believe that there are various degrees in the extent of the overriding of the pulmonary artery. In the original case of Taussig and Bing and that of Lev and Volk, the pulmonary artery arose primarily from the right ventricle. In our cases, the pulmonary artery originated mainly from the left ventricle.

A discussion of a transposition complex, whether complete or incomplete, always leads to speculation about the exact embryologic cause of this fascinating anomaly. A number of theories have been proposed. In our cases we shall briefly comment upon the most recent hypotheses.

The ingenious phylogenetic conception of Spitzer[22] has been attacked on the ground that his explanation of the abnormalities is complex and often too radical. As applied to our cases, it is difficult for us to accept the opinion of Spitzer that the aorta is not a transposed vessel but a right reopened aorta and that the pulmonary artery is thrown into what is apparently a left ventricle by a false anterior septum. No case has yet been reported in the literature in which two definite aortas, right and left, were present. Among the various types of transpositions as set forth and graded by Spitzer, it is impossible to find one which would conform to our cases. According to Spitzer, the aorta, being a right reopened ventricular aorta, always lies to the right of the crista supraventricularis. The latter, becoming hypertrophied and rotated into the plane of the preserved true posterior septum, takes the place of the true anterior septum, which has completely disappeared. Hence the pulmonary artery is transposed only apparently. Its ostium is on the left of the crista supraventricularis (false anterior septum) and on the right of the remnants of the true anterior septum and consequently it only appears to be in the left ventricle. We would be very reluctant to accept such an explanation in our cases. We can not accept the concept that the interventricular septum is in our cases anything but the normal one. We can not accept the belief that the crista supraventricularis must always separate the pulmonary artery from the aorta. Nor can we accept the view that the heavy muscular ridge described in our cases and interpreted as the crista supraventricularis is the hypertrophied right leaf of the bulboatrial ledge found in the primitive heart cavity.

The ontogenetic inversion theory of Pernkopf and Wirtinger and the recent hypothesis advanced by Lev and Saphir could satisfactorily explain our cases. The two theories differ in that the two German investigators assume that "the essential factors in transposition lie in pure ontogenetic embryological malformation" while the American authors retain in their conception the irritative hydrodynamic factors postulated by Spitzer. On the other hand, both theories admit that transposition complexes are related to abnormal absorption of the bulbus, a process occurring during the second phase of the development of the heart.

Pernkopf and Wirtinger's theory, founded on the concept of inversion, postulated that in the second phase of development of the heart a partial inversion (counterclockwise rotation) of the septal anlage occurs in the bulbar region, resulting in the various types of partial and complete transpositions.

Faulty absorption of the bulbus, due to an assumed abnormality of the ridge formation, according to Lev and Saphir, is responsible for the incorrect origin of the aorta and pulmonary artery and for the unequal size of the vessels. The various degree of pulmonary overriding in the reported cases could be explained satisfactorily by abnormal play of the hydrodynamic forces responsible for the bulbar torsion at the two ostia bulbotruncare and ventriculobulbare in the presence of a more marked abnormality of the ridge formation. The markedly different architecture of the conus found in the case of Lev and Volk could possibly be explained by a lesser degree of transposition. Proof of this would be offered by the course of the coronary arteries in this case and in our first two cases. In the former, the process of transposition of the coronary arteries is only partial, while in the latter it has been completed in that all branches of the left coronary artery arise from the original right coronary orifice.

The circulation in the Taussig-Bing complex is inconsequential during fetal life. With establishment of the pulmonary circulation the blood flow becomes distinctly unphysiologic. Systemic venous blood enters the right heart normally. It then flows from the right ventricle into the aorta and the overriding pulmonary artery. The amount and the direction of the shunt is dependent upon the pressures in the two circulations;

the flow always taking the path of least resistance. The magnitude of the shunt is also dependent upon the degree of overriding of the pulmonary artery. The pulmonary resistance, becoming lower than the systemic, permits a greater flow of blood into the lesser circulation, at least in the early stages of the disease.* The blood returning from the lungs through the pulmonary veins enters the left side of the heart normally. A greater portion flows into the pulmonary artery and the remainder into the right ventricle through the ventricular communication. Admixture of arterial and venous blood occurs at the level of the defect, which explains the difference in oxygen saturation in the right and left ventricle, aorta and pulmonary artery. The oxygen saturation of the pulmonary artery blood is the highest since the greater part of its blood comes from the left ventricle. The right ventricular blood has a lower oxygen saturation since the volume of the venous blood is much greater than the volume of arterial blood shunted from the left ventricle. The aortic blood has the lowest oxygen saturation because it consists almost entirely of venous blood reaching the aorta directly from the inflow portion of the right ventricle. The crista supraventricularis, acting as a false septum between the infundibulum and the region of the interventricular septal defect, somewhat hinders the flow of the shunted arterial blood from reaching the aorta. The myocardium is consequently supplied with blood poorest in oxygen content. The abnormality of hemodynamics throws light upon the anatomic findings. The work load of the right ventricle consists of the systemic and pulmonary resistances in addition to an increased volume of blood due to the left to right shunt. Consequently the right ventricle is markedly hypertrophied. On the other hand, the work load of the left ventricle is much less. It consists of the pulmonary resistance and a markedly increased volume of blood from the augmented pulmonary venous return and the right to left shunt. Therefore the left ventricular cavity is dilated with normal or slightly hypertrophied walls.

The prominent clinical sign of the Taussig-Bing syndrome is the cyanosis present from birth or its appearance shortly thereafter within the first few hours or days. It is the inevitable result of the anatomic structure of the heart. It is a permanent sign and almost always progressive. Clubbing of the fingers and toes and polycythemia develop in cases of sufficient survival. An outstanding feature of our cases was the intense dyspnea from the birth. We believe that the intracardiac hemodynamics, as governed by the anatomic structure of the right ventricle, was partially responsible for the labored breathing. The crista supraventricularis, forming a fairly deep partition between the defect of the ventricular septum, posteriorly located, and the anteriorly placed infundibulum, prevented the shunted arterial blood from being fully delivered to the aorta. Therefore the oxygen supplied to the systemic circulation was from the caval blood augmented by that portion of the shunted arterial blood which could by-pass the crista. Another important causative factor in the rapid, shallow breathing was that of the stimulating effect of the severe pulmonary congestion upon the intrapulmonary vagal endings. Holman and Beck[23] and Churchill and Cope[24] have given experimental proof of this phenomenon. Chiechi[25] has offered clinical evidence of this theory in patients with tetralogy of Fallot undergoing correction of the pulmonary stenosis by the method of Brock in which overcorrection of the pulmonary stenosis caused a marked increase of the pulmonary blood flow.

The next prominent finding is the radiologic picture of increased pulmonary circulation with hyperpulsatile hilar vessels that frequently amount to a hilar dance. On x-ray the heart is enlarged and has a globular configuration with an apparently normal pedicle in the posteroanterior and both oblique projections. There is often a diffuse systolic murmur of no diagnostic significance heard over the precordium, usually not loud, and occasionally accompanied by a thrill. Some authors[3,12] describe a booming, sharp pulmonary second sound. The electrocardiographic findings are those of right ventricular hypertrophy. The pronounced hypoxemia accounts for the stunting of growth and failure to gain weight almost invariably seen in these patients. The worsening of the clinical condition is manifest by symptoms and signs of high output cardiac failure, that is, rapid respirations, rapid heart rate, pulmonary and hepatic congestion. The course of the failure is seldom controlled with medical therapy.

The diagnosis of the Taussig-Bing anomaly is extremely uncertain in the living patient. We

* Our experience with patients who had marked signs and symptoms of a large pulmonary blood flow suggests that the lesser circulation reacted as a low-resistance circuit.

have already mentioned some of the difficulties commonly encountered to an endeavor to establish the diagnosis *in vivo*. The conditions from which this malformation must be differentiated include all the congenital heart anomalies with cyanosis and increased pulmonary blood flow. These are: complete transposition of the great vessels with ventricular septal defect, single ventricle with or without transposition, truncus communis persistens overriding a defect of the ventricular septum and its variants, truncus solitarius aorticus and truncus solitarius pulmonalis, and the Eisenmenger complex.

No difficulty should arise in the differential diagnosis with the last condition in which the cyanosis is ordinarily of late development. Another important point is that in the Taussig-Bing syndrome "exercise results in a fall in oxygen consumption whereas in the Eisenmenger complex there is an increase in oxygen consumption per liter of ventilation."[9]

In both truncus communis persistens overriding an interventricular communication with circulation to the lungs by way of pulmonary arteries and in truncus solitarius pulmonalis, the increased pulmonary blood flow is commonly accompanied by minimal or even absent cyanosis. A distinctive "sitting duck" silhouette is found on x-ray in truncus communis persistens. When the pulmonary blood supply is derived from the bronchial arteries, as found in the variant, truncus solitarius aorticus, the cyanosis is severe. In this condition, however, the vascularity of the lungs is commonly decreased with a reticular and stippled pattern distinctly characteristic and consequently diagnostic.

A single ventricle with transposition of the great vessels, the pulmonary artery arising from the common ventricle and the aortic from the rudimentary outlet chamber, shows greatly enlarged hilar shadows on x-ray. However cyanosis is slight or absent even though there is an increased amount of reduced hemoglobin in the arterial blood. On the other hand, in the case of a single ventricle with the aorta arising from the common chamber and the pulmonary artery from the rudimentary outlet chamber, the cyanosis tends to be severe but the pulmonary blood flow and lung vascularity is reduced.

Differentiation of the Taussig-Bing complex from complete transposition of great vessels with interventricular septal defect often represents an insoluble diagnostic problem. On purely clinical grounds the two conditions are identical and can not be separated. The x-ray findings in the Taussig-Bing syndrome are significant and they might be of diagnostic aid. Taussig[26] states that in complete transposition of great vessels, "in the antero-posterior position there is a . . . narrow aortic shadow. In the left anterior oblique position the shadow increases in width." The anatomic arrangement of the great vessels, ascending almost parallel to each other from the base of the heart, is responsible for this classic roentgen picture, of which variants have been described[27,28] since the first report given by Taussig.[29] In our cases the shadow cast by the great vessels appeared normal (Fig. 11) or enlarged (Fig. 12) and rotation of the patient in the left anterior oblique position failed to increase its width, the diagnosis of transposition was therefore not entertained in three of the four cases because the sign of Taussig could not be established. The absence of this finding in the anomaly under discussion is explained by the fact that when the pulmonary trunk overrides a defect of the ventricular septum, it is located posteriorly and to the left of the aorta. Furthermore, it is tremendously enlarged, and extends beyond the left margin of the ascending aorta. These two elements account for the absence of Taussig's sign in the Taussig-Bing complex. In a cyanotic child with the clinical findings of transposition of great vessels and the fluoroscopic findings just described the Taussing-Bing complex should be strongly suspected.

The importance of angiocardiography has been stressed as a means of definitely establishing the diagnosis of the anomaly. In very favorable conditions the biventricular origin of the pulmonary artery can be demonstrated in a lateral angiogram and the extent of its overriding can be approximately estimated. This unique feature is pathognomonic and should differentiate the Taussig-Bing heart from any other transposition complex and from any other congenital anomaly. The Swedish investigators[4] have given criteria for the classification of the various degrees of overriding of the aorta in tetralogy of Fallot. These criteria can be applied to the position of the pulmonary root in relation to the septum in the Taussig-Bing syndrome. Kjellberg and Coll reported only one case in their book in which the interventricular septum and on overriding pulmonary artery is readily visualized. In none of the other published angiograms of the Taussig-Bing syndrome can the biventricular origin of the pulmonary root be

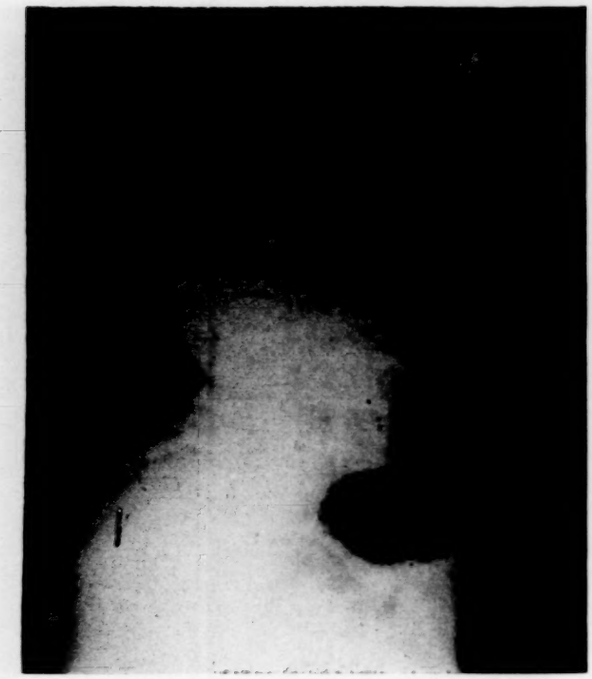


FIG. 11. Normal aortic pedicle in Case I.

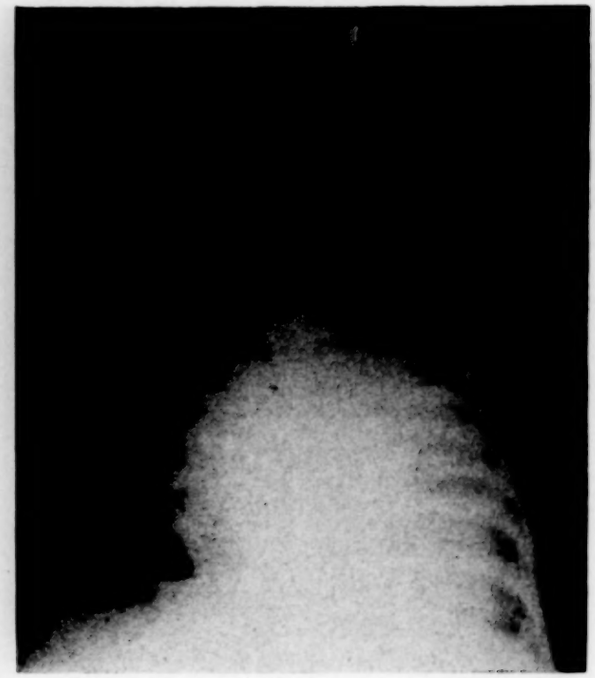


FIG. 12. The shadow of the great vessels is increased in width because of the greatly enlarged pulmonary artery (Case IV).

definitely ascertained following the standards established by the Swedish investigators.

It has been maintained that the overriding pulmonary artery may advantageously influence the course and prognosis of the disease, in contrast to other transposition complexes.[9] This has not been the case in our patients since all died very early with an identical clinical picture. We believe that the factor which may alter the prognosis is not the overriding in itself but its extent. When the pulmonary artery arises primarily from the right ventricle there is apparently a longer survival. When the pulmonary artery originates mainly from the left ventricle, as in our patients, the prognosis is apparently poor. In this situation the prognosis will depend upon another factor, that is, the size of the interventricular communication, as in complete transposition.

According to a still highly controversial and somewhat teleologic theory eleborated by Edwards and his associates,[31–34] the key to the prognosis would seem to reside in the role played by the pulmonary vascular bed in governing the pulmonary blood flow. When at birth a "common ejectile force" * is present in the heart, due to a large interventricular communication, the pulmonary vascular bed may follow three possible courses.[35,36] First, the pulmonary vasculature may evolve normally, with a decreased peripheral pulmonary resistance. Therefore a progressively larger portion of cardiac output passes to the lesser circulation and a proportionally smaller amount reaches the systemic circulation. This, in turn causes an increase in the cardiac output to maintain a normal blood flow, since the systemic resistance remains unchanged. The clinical picture of high output cardiac failure ensues and the patient dies in spite of all medication. Secondly, if the fetal condition of high pulmonary vascular resistance continues after birth, balancing the blood flow in the two circulations, † the patient may be symptom-free with minimal or absent cyanosis. And lastly, if

* The Taussig-Bing complex, according to this view, belongs to a group of congenital heart disease with large defects between the ventricles or great vessels (Eisenmenger complex, transposition of the great vessels without pulmonary stenosis, coarctation of the aorta proximal to a patent ductus arteriosus, common ventricle without pulmonary stenosis, tricuspid atresia without pulmonary stenosis) in which there is a common ejectile force for the systemic and lesser circulation. The distribution of the blood into the two circuits is therefore dependent upon their respective peripheral vascular resistance.

† This, according to Edwards, may occur because the thick-walled, small-lumened arterioles of the fetal lungs maintain their peculiar structure after birth and normal vascular evolution does not occur.

there is a gradual increase of the pulmonary vascular resistance with secondary intimal changes in the small pulmonary arteries, the pulmonary resistance may become greater than the systemic and the patient suffers hypoxia, becoming cyanotic and dyspneic.

Histologic examination of the lungs in our second case showed that the pulmonary vasculature had followed the pattern of normal postnatal evolution. The structure of the small muscular arteries was consistent with the normal. There was an increase in the lumen of the vessels and decrease of the thickness of the medial coat. Therefore, in this case the lesser circulation had reacted hemodynamically as a low-resistance circuit, and this led to high output failure. In the other three cases, however, the small muscular arteries of the lungs showed the medial thickening and narrow lumen characteristic of the fetal state. In the twenty-three month old child a rare vessel exhibited intimal change as well. Yet in these cases the hemodynamic response of the pulmonary vascular bed was that of a low-resistance area in spite of the fetal structure of the vessels. A state of balance between the lesser and great circulation was not reached and the patients died of the characteristic congestive heart failure described. It is important to keep in mind that in the period from birth to six months the pulmonary vessels in patients with congenital abnormalities characterized by a "common ventricular ejectile force" may be difficult to distinguish from those in the normal subject before postnatal changes have occurred.[37]

TREATMENT

Surgical correction of the Taussig-Bing complex is linked intimately to the surgical treatment of transposition of the great vessels. Many procedures have been proposed for the correction of this anomaly but all of them have been associated with a high mortality.[38–40] Restoration of normal anatomy by surgical retransposition of the great vessels with transplantation of coronary arteries would be the ideal operation.[41] Attempts in this direction are currently being made.[42] Reestablishment of a quasi-normal anatomic relationship, however, could be achieved by creating a "corrected transposition." This procedure, which entails the transposition of the systemic veins to the left atrium and the pulmonary veins to the right atrium, has been attempted with unsatisfactory results.[43] Another method of obtaining a form of "corrected" transposition is that proposed by Albert.[44] By remodeling and shifting the interatrial septum in two planes, the caval blood is diverted into the left atrium and the pulmonary return into the right atrium. This procedure has had only experimental trial.

In addition to the technical problems involved in the surgical correction of pure transposition of great vessels, the Taussig-Bing complex presents the disadvantage of a large interventricular communication and a variable degree of overriding of the pulmonary artery. Ventricular septal defects are currently being closed successfully under direct vision by means of open cardiotomy. The overriding should constitute no substantial obstacle to the repair of the defect, since the author has been able to correct the septal lesion in the fresh dead heart of the first case employing the technic of Lillehei.[45] In the cases of pulmonary artery arising primarily from the right ventricle, suture of the inferior margin of the defect to that portion of the atrioventricular annulus displaced in the right ventricular cavity might encroach upon the left ventricular outflow.

With the advent of definitive intracardiac surgery with total cardiac and pulmonary by-pass utilizing controlled cross circulation,[46–48] continuous arterial reservoir perfusion[49] or pump oxygenator,[50] adequate methods appear available for performing successfully any one of the operations mentioned. Thus the transposition complexes, perhaps the most fatal and challenging of congenital malformations, may yet be conquered by modern surgery.

SUMMARY

A clinical and pathologic study of four cases of Taussig-Bing complex is presented. The abnormal anatomy of the right ventricular cavity is described in detail in the first two cases.

A review of the pertinent literature is given, with critical observations on the reported cases.

After a brief comment on the embryology of the malformation, the hemodynamic and clinical implication of the syndrome are discussed.

The differentiation from other congenital abnormalities characterized by cyanosis and increased pulmonary blood flow is reviewed.

The various prognostic factors are considered and a short account is given of the available surgical procedures for the correction of the abnormality.

ADDENDUM

Since this paper was written, a report of two more cases of Taussig-Bing complex has appeared in the literature.[51] The diagnosis of Taussig-Bing heart was suspected clinically in both instances. In the first case it was confirmed by angiocardiography while in the second by catheterization studies.

We are not in agreement with the authors' interpretation of the angiocardiograms (Case I) and the catheterization findings (Case II). The angiocardiographic plates exhibited in the first case do not show the pathognomonic sign of the syndrome, that is, the biventricular origin of the pulmonary artery. They merely show a simultaneous opacification of the aorta and pulmonary artery which can also occur in transposition of the great vessels with a large interventricular septal defect. The catheterization findings in the second case are far from being "entirely conclusive" as the authors state. The finding of blood oxygenation greater in the pulmonary artery than in the aorta and the recording of similar systolic pressures in both great vessels and right ventricle are not typical of a Taussig-Bing heart and can be explained equally well by a transposition of the great vessels with an interventricular septal defect.

Acknowledgment: The author wishes to express his gratitude to Dr. N. A. Antonius, Director of the Cardiology Department and Dr. R. Miller for their suggestions in the preparation of the manuscript. The author feels especially indebted to Dr. S. J. Rose, Chief of Pathology, and Miss Antoniette Criscitiello for their invaluable assistance and cooperation. Dr. J. E. Edwards, Section of Pathology, Mayo Clinic, kindly reviewed the microscopic sections of the lungs.

REFERENCES

1. Taussig, H. B. and Bing, R. J. Complete transposition of the aorta and a levoposition of the pulmonary artery. *Am. Heart J.*, 37: 551, 1949.
2. Abbott, M. E. Atlas of Congenital Heart Disease. New York, 1936. The American Heart Association.
3. Metianu, C. et al. Taussig-Bing syndrome diagnosed *in vivo* and verified by autopsy; new case. *Acta cardiol.*, 8: 76, 1953.
4. Kjellberg, S. R., Mannheimer, E., Rudhe, U. and Jonsson, B. Diagnosis of Congenital Heart Disease. Chicago, 1955. Year Book Publishers, Inc.
5. Coppoletta, J. M. and Wolbach, S. B. Body length and organ weights of infants and children. *Am. J. Path.*, 9: 55, 1933.
6. Pernkopf, E. and Wirtinger, W. Die Transposition der Herzostien. Ein Versuch der Erklärung dieser Erscheinung. *Ztschr. f. Anat. u. Entwcklngsgesch.*, 100: 563, 1933.
7. Pernkopf, E. Der partielle Situs inversus der Eingeweide beim Menschen. *Ztschr. f. Anat. u. Entwcklngsgesch.*, 79: 577, 1926.
8. Brown, J. W. Congenital Heart Disease, p. 193. London, 1939. Staples Press.
9. Brown, J. W. Congenital Heart Disease, p. 264. London, 1950. Staples Press.
10. Lev, M. and Volk, B. W. The pathological anatomy of the Taussig-Bing heart; riding pulmonary artery; report of a case. *Bull. Int. A. M. Museums*, 31: 54, 1950.
11. Van Buchem, F. S. F., Van Vermeskerkew, J. L. and Orie, N. S. M. Transposition of the aorta (Taussig's syndrome). *Acta med. Scandinav.*, 137: 66, 1950.
12. Bayer, O. Das Syndrom von Taussig und Bing. *Schweiz. med. Wchnschr.*, 81: 558, 1951.
13. Martin, J. A. and Lewis, B. M. Transposition of the aorta and levoposition of the pulmonary artery. *Am. Heart J.*, 43: 621, 1952.
14. Maxwell, G. G. and Crumpton, C. W. The Taussig-Bing syndrome; a report of two further cases, one complicated by aortic coarctation. *Am. J. Med.*, 17: 578, 1954.
15. Espino Vela, J. El complejo de Taussig-Bing; estudio clinico de un caso. *Arch. Inst. cardiol. México*, 25: 89, 1955.
16. Moragues, V. and Lynxwiler, C. P. Cardiac Anomalies. A Clinico-pathologic Correlation. Baltimore, 1954. Williams & Wilkins Co.
17. Lev, M. and Saphir, O. A theory of transposition of the arterial trunks based on the phylogenetic and ontogenetic development of the heart. *Arch. Path.*, 39: 172, 1945.
18. Edwards, J. E. Taussig-Bing complex. In: Gould, S. E. Pathology of the Heart, p. 338. Springfield, Ill., 1953. Charles C Thomas.
19. Campbell, M. and Suzman, S. Transportation of the aorta and pulmonary artery. *Brit. Heart J.*, 12: 201, 1950.
20. Gasul, B. M. and Marienfeld, C. J. Clinical diagnosis of the cyanotic types of congenital malformations of the heart. *Pediat. Clin. North America*, 1: 131, 1954.
21. Keith, J. D. Angiocardiography in infants and children. *Pediat. Clin. North America*, 1: 73, 1954.
22. Spitzer, A. In: Lev. M. and Vass, A. The Architecture of Normal and Malformed Hearts. Springfield, Ill., 1951. Charles C Thomas.
23. Holman, E. and Beck, C. S. The physiological response of the circulatory system to experimental alteration. III. The effect of aortic and pulmonary stenosis. *J. Clin. Investigation*, 3: 283, 1926.
24. Churchill, E. D. and Cope, O. The rapid shallow breathing resulting from congestion and edema. *J. Exper. Med.*, 49: 531, 1929.
25. Chiechi, M. A. La tetralogia di Fallot. I. Considerazioni embriologiche e anatomo-patologiche. Tecnica operativa ad analisi di 19 casi sottoposti all'operazione di Brock. *Chir. torac.*, 6: 277, 1953.
26. Taussig, H. B. Congenital malformations of the heart. The Commonwealth Fund, New York, 1947.

27. Astley, R. and Parson, C. Complete transposition of the great vessels. *Brit. Heart J.*, 14: 13, 1952.
28. Castellanos, A., Pereira, R. and Garcia, O. Angiocardiography: anatomoroentgenological forms of transposition of the great vessels. *Am. J. Roentgenol.*, 64: 255, 1950.
29. Taussig, H. B. Complete transposition of the great vessels: clinical and pathologic features. *Am. Heart J.*, 16: 728, 1938.
30. Edwards, J. E. Transposition of great vessels. In: Gould, S. E. Pathology of the Heart, p. 339. Springfield, Ill., 1953. Charles C Thomas.
31. Edwards, J. E. Structural changes of the pulmonary vascular bed and their functional significance in congenital cardiac disease. 26th Ludwig Hektoen Lecture. *Proc. Inst. Med. Chicago*, 18: 134, 1950.
32. Civin, W. H. and Edwards, J. E. The postnatal structural changes in the intrapulmonary arteries and arterioles. *Arch. Path.*, 51: 192, 1951.
33. Edwards, J. E. Functional pathology of congenital cardiac disease. *Pediat. Clin. North America*, 1: 13, 1954.
34. Edwards, J. E. Pathologic considerations in adjustments between the systemic and pulmonary circulations. In: Henry Ford Hospital Symposium on Cardiovascular Surgery. Philadelphia, 1955. W. B. Saunders Co.
35. Damman, J. F., Jr. and Muller, W. H., Jr. The role of the pulmonary vascular bed in congenital heart disease. *Pediatrics*, 12: 307, 1953.
36. Damman, F. J., Jr. and Ferencz, C. Adjustments between the systemic and pulmonary circulations: clinico-anatomic correlations. In: Henry Ford Hospital Symposium on Cardiovascular Surgery. Philadelphia, 1955. W. B. Saunders Co.
37. Edwards, J. E. Personal communication.
38. Hanlon, C. R. and Blalock, A. Complete transposition of the aorta and the pulmonary artery. Experimental observation on venous shunts as corrective procedures. *Ann. Surg.*, 127: 385, 1948.
39. Blalock, A. and Hanlon, C. R. The surgical treatment of complete transposition of the aorta and the pulmonary artery. *Surg., Gynec. & Obst.*, 90: 1, 1950.
40. Blalock, A. A consideration of some of the problems in cardiovascular surgery. *J. Thoracic Surg.*, 21: 543, 1951.
41. Fell, E. H. and Forney, R. A. Surgical treatment of congenital cardiovascular anomalies accompanied by cyanosis. *Pediat., Clin. North America*, 1: 197, 1954.
42. Keith, J. D., Neill, C. A., Vlad, P., Rowe, R. D. and Chute, A. L. Transposition of the great vessels. *Circulation*, 7: 830, 1953.
43. Lillehei, C. W. and Varco, R. L. Certain physiologic, pathologic, and surgical features of complete transposition of the great vessels. *Surgery*, 34: 376, 1953.
44. Albert, H. A. Surgical correction of transposition of the great vessels. In: Surgical Forum—Clinical Congress of the American College of Surgeons, vol. 5, p. 74. Philadelphia, 1954. W. B. Saunders Co.
45. Lillehei, C. W., Cohen, M., Warden, H. E., Ziegler, N. R. and Varco, R. L. The result of direct vision closure of ventricular septal defects in eight patients by means of controlled cross-circulation. *Surg., Gynec. & Obst.*, 101: 446, 1955.
46. Lillehei, C. W., Cohen, M., Warden, H. E. and Varco, R. L. The direct vision intracardiac correction of congenital anomalies by controlled cross-circulation. Results in thirty two patients with ventricular septal defects, tetralogy of Fallot and atrioventricularis communis defects. *Surgery*, 38: 11, 1955.
47. Warden, H. E., Cohen, M., Read, R. C. and Lillehei, C. W. Controlled cross-circulation for open intracardiac surgery. *J. Thoracic Surg.*, 28: 331, 1954.
48. Lillehei, C. W., Cohen, M., Warden, H. E., Read, R. C., De Wall, R. A. Aust, J. B. and Varco, R. L. Direct vision intracardiac surgery. In: Henry Ford Hospital International Symposium on Cardiovascular Surgery, p. 371. Philadelphia, 1955. W. B. Saunders Co.
49. Warden, H. E., Read, R. C., De Wall, R. C., Aust, J. B., Cohen, M., Ziegler, N. R., Varco, R. L. and Lillehei, C. W. Direct vision intracardiac surgery by means of a reservoir of "arterialized venous" blood. *J. Thoracic Surg.*, 30: 649, 1955.
50. Du Shane, J. W., Kirklin, J. W., Patrick, R. T., Donald, D. E., Terry, H. R., Jr., Burchell, H. B. and Wood, E. H. Ventricular septal defects with pulmonary hypertension. *J. A. M. A.*, 160: 950, 1956.
51. de Carvalho Azevedo, A., Wey Toledo, A., Alves de Carvelho, A. and Roubach, R. Transposition of the aorta and levoposition of the pulmonary artery—Taussig-Bing Syndrome. *Am. Heart J.*, 52: 249, 1956.

The Cardiac Output in Paget's Disease before and after Treatment with Cortisone*

ELLIOT RAPAPORT, M.D.,† HIROSHI KUIDA, M.D.,‡ LEWIS DEXTER, M.D.,
PHILIP H. HENNEMAN, M.D. *and* FULLER ALBRIGHT, M.D.

Boston, Massachusetts

CARDIAC output in patients with extensive Paget's disease may be considerably elevated.[1,2] The observation by two of us (P. H. H. and F. A.) that large doses of cortisone and ACTH suppress the activity in Paget's disease led us to investigate the effect of this therapy on the cardiac output. The clinical results of treatment in these patients are reported elsewhere.[3]

METHODS AND PROCEDURES

Fifteen studies were performed on six patients with extensive osteitis deformans. Three patients had three studies and three patients had two studies with no uniformity in the type and dosage of hormone treatment nor in the relation of duration of therapy to time of study. (Table 1.) Cardiac output was measured immediately before and from nine to sixty-one days after initiation of cortisone therapy in four cases. Patient A. M. had been on low doses of hydrocortisone for one year before the first cardiac output determination. She was restudied after twenty-five days of therapy with high doses of cortisone and again eighty-six days after resumption of low maintenance doses of cortisone. The second study in patient E. C. was performed four days after discontinuation of thirty-five days of therapy. Patient A. F. was studied before therapy, after six days of high doses followed by thirty-one days of lower doses of cortisone, and again after two hundred fifty days on maintenance dosage. The earliest study following institution of treatment was performed on patient G. G., who was studied after receiving 160 mg. prednisone over a three-day period and a third time after ninety-two days on 20 mg. prednisone per day. All patients were on salt restriction diets during the period of high-dosage cortisone therapy. Determinations were made with the patient fasting and at rest in the recumbent position. Cardiac output was determined by the indicator dilution method,[4] using Evans blue dye§ and on two occasions I-131 labeled human serum albumin. The validity of this method with particular reference to peripheral vein injection has been adequately tested elsewhere.[5–7] In our laboratory, the average of all individual ratios of Evans blue dye flows to direct Fick method cardiac outputs is .96 (σ = .12). A Gibson syringe, calibrated by weight to deliver a known volume, was used to inject approximately 10 mg. of Evans blue dye or 15 microcuries of radioactivity into an antecubital vein during the midpoint of a three-minute collection of expired air for oxygen consumption. Samples were collected from the contralateral brachial artery every two seconds through a short segment of polyethylene tubing into a specially constructed rotary multiple-sampling device. Dye analyses were performed on undiluted plasma with microcuvettes‖ in a Beckman DU spectrophotometer at 620 mμ. Plasma flow was converted to blood flow using the large-vessel hematocrit corrected for trapped plasma.[8] Ten and twenty minute blood samples were taken for determination of total plasma volume, which was converted to total blood volume with the same hematocrit. In two cases where I-131 albumin was used as the indicator, radioactivity was determined to 1 per cent statistical accuracy in measured whole blood aliquots of each sample and in duplicate 1 cc. aliquots of a 1:1000 dilution of the

§ Courtesy Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, Ind.

‖ Pyrocell Manufacturing Company, New York, N. Y.

* From the Medical Clinic, Peter Bent Brigham Hospital, the Department of Medicine, Massachusetts General Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts. Work was supported in part by grants to Dr. Dexter from the Life Insurance Medical Research Fund and the National Heart Institute, U. S. Public Health Service (grant H-450); and to Dr. Albright from the U. S. Public Health Service (grants C-1887 and A-605), the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council, the Rockefeller Foundation, and Ayerst, McKenna and Harrison, Ltd.

† This work was done during the tenure of an American Heart Association Fellowship. Present address: Veterans Administration Hospital, Albany, New York.

‡ This work was done during the tenure of a Postdoctorate Fellowship from the National Heart Institute, U. S. Public Health Service and currently a Fellowship from the American Heart Association.

injected solution. Since activity was measured in whole blood, a conversion to blood flow was not necessary. Direct intra-arterial pressures were recorded with each output. Total systemic resistance was determined by the formula

$$R = \frac{\text{mean arterial pressure (mm. Hg)} \times 1{,}332}{\text{cardiac output (cc./sec.)}}.$$

A derived arterio-mixed venous oxygen difference was calculated with each output by the formula

$$\text{Arteriovenous oxygen difference} = \frac{\text{oxygen consumption (cc./min.)}}{\text{cardiac output (liters/min.)}}.$$

Bone surveys were taken on each patient to estimate the degree of skeletal involvement with Pagetis disease. At the same time, serum alkaline phosphatase determinations were also made.

RESULTS

Resting cardiac output prior to therapy was distinctly elevated in all patients. (Fig. 1, Table 1.) With the administration of large doses of cortisone for a sufficient duration, cardiac output fell in each case to levels which were within the normal range for this laboratory.[9] In patient G. G. there was no change in cardiac output after three days of high doses of prednisone, but 101 days after institution of treatment the output was low normal. In patients A. F. and A. M. studies performed after long-term maintenance doses of cortisone showed a return of cardiac output to high pretreatment levels with a concomitant rise in alkaline phosphatase levels. The fall in cardiac output ranged from 13 to 52 per cent of pretreatment values, averaging 37 per cent (σ = 4.3). The mean of the individual ratios of pretreatment to posttreatment cardiac outputs was 1.63 (σ = .31). The drop in cardiac output was not associated with any consistent change in oxygen consumption; the average of the ratio of pretreatment to posttreatment oxygen consumptions in individual patients was 1.04 (σ = .20). Treatment had no consistent effect on the pulse pressure, mean arterial pressure, large vessel hematocrit or total blood volume. The pulse rate distinctly slowed in three patients treated with cortisone and remained essentially unchanged in the remaining three. In all cases total systemic resistance increased with treatment. The derived arteriovenous oxygen difference was initially low in all cases and rose toward normal following treatment. In two cases (A. M. and A. F.) cardiac output was redetermined after reduction of cortisone dosage to maintenance levels for eighty-six to two hundred fifty days, respectively. Cardiac output, which had dropped to normal levels with treatment, was again elevated to pretreatment levels. (Table 1.)

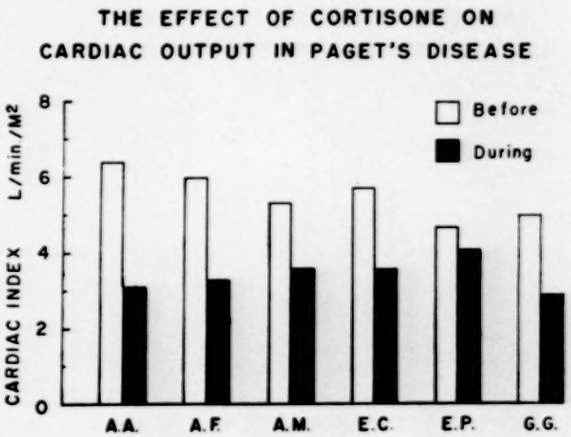


FIG. 1.

COMMENTS

Edholm, Howarth, and McMichael in 1945[1] first demonstrated that the cardiac output may be elevated in Paget's disease. Subsequent studies by Howarth[2] in a larger series of patients indicated that an increased cardiac output was not an indubitable finding, for it was not present in patients in whom alkaline phosphatase levels were below 45 K.A. units or when less than 35 per cent of the skeleton was involved by disease. Edholm and Howarth[10] also studied the peripheral circulation in Paget's disease. They demonstrated a marked increase in bone vascularity of abnormal bone compared to normal bone, as evidenced by bone arteriographs. They also demonstrated an increased blood flow in involved bones, as judged by a somewhat crude but ingenious method for measuring humeral bone flow. These authors concluded, therefore, that an elevated cardiac output in this condition was the result of an increased blood flow in involved bones. The actual mechanism of the increased blood flow has yet to be proved, but they suggested that Paget's disease acts in a manner analogous to a peripheral arteriovenous fistula except that the shunting of blood from the arteries to the veins occurs in bones of affected areas: (1) When the circulation to an affected extremity involved with Paget's disease is occluded, the pulse slows and the diastolic blood pressure rises;[1] these changes are similar to

TABLE 1

Patient's Initials, Age and Sex	Day of Determination with Respect to Therapy	Drug Dosage (mg./day)	Weight (kg.)	Body Surface Area (sq. meter)	Serum Alkaline Phosphatase (Bodansky units)	Cardiac Index (L./min/sq. meter)	O_2 Consumption Index (cc./min./sq. meter)	Derived Arteriovenous Oxygen Difference (cc./L.)	Heart Rate/Min.	Intra-arterial Pressure (mm. Hg)		Total Systemic Resistance (dynes sec. cm.$^{-5}$)	Total Blood Volume (cc.)	Total Blood Volume (cc./kg.)	Hematocrit (%)
										Systolic/ Diastolic	Mean				
A. A., 45, M	Before therapy	...	87.0	2.06	38	6.4	155	24.4	88	132/71	98	673	.....	.....	45
	9 days with cortisone	600	87.5	....	23	3.1	168	55.1	52	149/75	95	1,206	4,457	51.2	39
A. F., 41, M	Before therapy	...	64.0	1.69	114	6.0	194	32.2	76	140/69	88	690	4,492	70.2	38
	6 days with cortisone, then	600	....	....	60	....	....	....	..	.....	....	.....	.....	.....	..
	31 days with cortisone	100	64.0	....	100	3.3	154	46.4	75	105/62	88	1,171	.....	.....	39
	250 days with cortisone	75	....	....	168	6.1*	....	....	74	125/63	82	637	.....	.....	37
A. M., 48, F	360 days with hydrocortisone	60	50.9	1.45	108	5.3	146	27.5	84	143/80	106	1,101	4,368	85.8	41
	25 days with cortisone	600	47.8	....	46	3.6	133	37.1	66	160/87	114	1,754	4,050	84.9	40
	86 days with cortisone	20	50.8	....	150	4.7	130	27.8	75	112/64	87	1,024	4,842	95.1	33
E. C., 69, F	Before therapy	...	56.8	1.47	33	5.7	156	27.3	86	135/55	90	857	4,379	77.1	37
	35 days with cortisone, then	600	....	....	....	....	....	....	..	.....	....	.....	.....	.....	..
	4 days without cortisone	0	51.0	....	13	3.6	126	35.1	76	141/65	98	1,479	4,101	80.5	39
E. P., 77, F	Before therapy	...	57.8	1.52	24	4.7	114	24.4	80	140/68	98	1,005	3,752	64.9	42
	56 days with prednisone	30	58.0	....	14	4.1	147	35.6	79	144/77	101	1,283	3,918	67.8	44
G. G., 53, F	Before therapy	...	51.8	1.48	17	5.0*	99	19.9	75	143/88	112	1,210	3,584	69.2	..
	1 day with prednisone, then	40	....	....	....	....	....	....	..	.....	....	....	.....	.....	..
	2 days with prednisone	60	....	....	....	5.1	107	21	78	149/85	113	1,190	3,622	69.9	40
	6 days with prednisone, then	60	....	....	....	....	....	.....	..	.....	.....	.....	.....	.....	..
	92 days with prednisone	20	52.2	....	6.1	2.9	109	37.7	78	164/111	131	2,437	3,778	72.4	43

* I-131 human serum albumin ("RISA") used as indicator.

those which occur when a peripheral arteriovenous aneurysm is manually occluded.[11] (2) The femoral arteriovenous oxygen difference is narrower in an involved extremity compared to an uninvolved homologue.[12]

Our observations confirm those of Howarth[2] that cardiac output in extensive Paget's disease is elevated. Cardiac output before treatment was elevated in all the cases studied. (Fig. 1, Table 1.) All five patients had, by x-ray, at least 30 per cent of their skeleton involved with Paget's disease. The lowest pretreatment alkaline phosphatase level was 17 Bodansky units (Patient E. P.), which is still considerably higher than the 45 K.A. unit level below which Howarth[2] was unable to find an elevated cardiac output. Lequime and Denolin[13] have recently reported their experience in seven cases of Paget's disease in which five patients had "generalized" involvement. These investigators were unable to find significant alterations in resting circulatory dynamics in their patients, although they con-

curred in the opinion that there is an increased blood flow in involved bones. In two of their patients exercise resulted in abnormal augmentations of cardiac output. It is difficult to explain the normal resting cardiac outputs in their patients in view of our own results and those of Howarth,[2] but these authors also pointed out that whether or not an increased cardiac output will be present depends on the extent and activity of the Paget's process. Unfortunately, alkaline phosphatase levels were not reported in their cases.

Accurate figures for normal total skeletal blood flow are not available to our knowledge. However, Bazett[14] has indicated that it must be less than 14 per cent of the total cardiac output. This figure is the residual percentage of cardiac output remaining after all measurable or estimable regional flows are subtracted from the total cardiac output. If one accepts the premise that the increased cardiac output in Paget's disease is a reflection of the increased flow through involved bones,[13] the difference in cardiac output before and during treatment with cortisone represents a quantitative approximation of the increased bone blood flow in our cases. Further, if it is assumed that the normal cardiac outputs uniformly observed with cortisone therapy reflect the reduction of bone blood flow to normal, one can utilize Bazett's figures to estimate that total bone blood flow in our cases, before therapy, was increased roughly 200 to 900 per cent.

Resting oxygen consumptions in our cases were not elevated in proportion to the rise in cardiac output. As a result, the derived mixed arteriovenous oxygen differences were narrowed. This suggests that the observed increased blood flow is not secondary to increased local metabolic activity. It is however consistent with the view that there may be an arteriovenous communication.

Figure 1 illustrates the effect of cortisone therapy on cardiac output. In each case cardiac output fell dramatically. The second study on patient G. G. was performed to determine how soon after institution of therapy the reduction in cardiac output occurs. The fact that the output did not change after three days of therapy, while it did in patient A. A. after nine days of treatment suggests that this occurs after about one week of treatment. The observation that cardiac output as well as serum alkaline phosphatase values returned to pretreatment levels in patients A. F. and A. M. after prolonged courses of low maintenance doses of cortisone suggests that suppression of activity does, indeed, depend on massive doses of hormone. The concomitant directional changes in cardiac output and alkaline phosphatase levels suggest that they are functions of the same abnormality, which in our interpretation is the activity of the disease.

The fall in cardiac output was not accompanied by any significant change in oxygen consumption. Consequently, the narrowed calculated pretreatment arteriovenous oxygen difference rose into the normal range with cortisone. This would indicate that possible depression of the general metabolic activity of these patients by cortisone was not a significant factor in the reduction of cardiac output.

Although the pulse pressure prior to therapy in these patients was somewhat widened, in confirmation of the observations of Kay,[15] there was no consistent decrease in pulse pressure with cortisone therapy. In this regard, the effects of cortisone were different from those resulting from acute occlusion of areas effected with Paget's disease from the circulation, where the pulse pressure decreases due to a rise in diastolic blood pressure. This difference may result from the fact that circulatory adjustments have time to occur during weeks of cortisone therapy, as contrasted to sudden circulatory occlusion. On the other hand, the possibility exists that the widened pulse pressure may be due primarily to the presence of atherosclerosis, which is known to occur more extensively and frequently in patients with Paget's disease compared with the normal population[16] rather than to possible arteriovenous communications.

The pulse rate in three patients appeared to slow appreciably with cortisone therapy. No change occurred in the remaining three patients. This slowing was particularly striking in patient A. A., in whom the fall in cardiac output was most marked; the pulse rate dropped from 88 to 52 beats per minute with cortisone therapy. This change may be likened to the so-called Nicoladoni Branham sign or slowing of the pulse rate with occlusion of a peripheral arteriovenous fistula.[11]

Total systemic resistance was low or low-normal in all cases before cortisone administration. This presumably reflects the low resistance of the vascular bed in the involved areas. Whether or not other regions of the body contribute to lowering of total systemic resistance is unknown,

since to our knowledge, aside from the bone flow studies already mentioned, regional blood flows have not been determined in Paget's disease. The rise in total systemic resistance with treatment may be the result of an increase in resistance of the vascular bed in the affected areas. Whether this might be due to anatomic obliteration or vasoconstriction is not known. Anatomic obliteration of the abundant vascular bed seems an unlikely explanation, since in patients A. M. and A. F. cardiac outputs determined several months after termination of large doses of cortisone had reverted back to pretherapy levels. In addition, evidence of clinical activity resumes in these patients once the suppressive influence of large doses of cortisone is removed.[3] Finally, biopsy specimens[3] from affected areas of the skull during treatment in each patient failed to show any anatomic obliteration of vascular channels when compared with pretreatment biopsy specimens.

Total blood volume in large arteriovenous fistulas tends to be elevated and returns toward normal with surgical obliteration.[17] Of the four patients with Paget's disease in whom total blood volume was determined before and during high dosage cortisone therapy, only one (A. M.) had a somewhat high pretreatment value. In one other (E. C.) it was at the upper limits of normal. In none of the patients, however, were the changes with cortisone therapy impressive. Two patients revealed a 7 and 6 per cent drop in total blood volume while in two others there was a 4 and 6 per cent increase from control values. These small changes in blood volume are probably within the experimental error of the method[18] and are less than that felt necessary to result, *per se*, in a change of cardiac output. The question arises as to whether or not the known salt and water retaining effects of cortisone are masking an otherwise apparent fall in total blood volume. However, Walser, Seldin, and Burnett[19] have shown that in patients treated with cortisone or ACTH and permitted even considerable salt intake an increase in plasma or blood volume will not develop although a considerable expansion of extracellular fluid space may occur.

The question naturally arises whether or not cortisone itself depresses cardiac output independently of its effect on the Paget's process. Information in the literature on the effect of cortisone in usual therapeutic doses on cardiac output is scanty. Perera[20] noted a slight reduction in cardiac output as determined with the ballistocardiograph in a hypertensive subject who received cortisone. Horowitz and his associates[21] also reported a mild decrease in cardiac output in patients with rheumatoid arthritis treated with cortisone. These patients had no gross evidence of cardiac disease and the effect on cardiac output was attributed to a decreased heart rate secondary to the improvement in the inflammatory disease. No studies have been reported, to our knowledge, on the effect of cortisone on other high output states. We have observed one patient with diffuse pulmonary cryptococcosis who had chronic severe hypoxia. Despite cortisone therapy, which the patient was receiving at the time of cardiac catheterization, cardiac output was markedly elevated.

The mechanism whereby cortisone therapy produces this dramatic effect on cardiac output in Paget's disease was not elucidated by these studies. If one accepts the fact that the increased cardiac output in Paget's disease is due to increased flow through involved bone, and further that this results from formation of numerous arteriovenous communications, it becomes necessary to explain how cortisone can, in effect, obliterate enough of these channels to result in a decrease in cardiac output. The anti-inflammatory effect of these agents is well documented, but the lesions in Paget's disease are not clearly of an inflammatory nature. In our cases biopsies of the skull before and during therapy have not clearly demonstrated changes in vascularity. The paucity of information on the general circulatory effects of such high doses of cortisone in normals and other high output states also adds to the difficulty in interpreting our data. This question of the mechanism by which cortisone reduces cardiac output in Paget's disease is therefore left open. Reliable determinations of regional flows and resistances of involved areas before and after therapy would narrow this problem, but methodology in this field to date is still quite inadequate.

SUMMARY

1. Observations on the cardiac output have been made in six patients with extensive Paget's disease before and during treatment with large doses of cortisone.

2. In all cases, cardiac output was elevated before treatment. High doses of cortisone for a sufficient duration, more than three days and less than nine days, produced a pronounced fall to normal levels. Serum alkaline phosphatase

levels changed in the same direction as the cardiac output.

3. Cortisone had no consistent effect on oxygen consumption, large vessel hematocrit, total blood volume, pulse pressure or mean arterial pressure. Cortisone therapy resulted in a pronounced drop in pulse rate in three of the six patients studied.

4. The mechanism through which cortisone exerts its effect on cardiac output in Paget's disease was not elucidated by these studies.

REFERENCES

1. Edholm, O. G., Howarth, S. and McMichael, J. Heart failure and bone blood flow in osteitis deformans. *Clin. Sc.*, 5: 249, 1945.
2. Howarth, S. Cardiac output in osteitis deformans. *Clin. Sc.*, 12: 271, 1953.
3. Henneman, P. H. and Albright, F. The suppression of Paget's disease with ACTH and cortisone. *Tr. A. Am. Physicians*, 68: 238, 1955.
4. Moore, J. W., Kinsman, J. M., Hamilton, W. F. and Spurling, R. G. Studies on the circulation. II. Cardiac output determinations: comparison of the injection method with the direct Fick procedure. *Am. J. Physiol.*, 89: 331, 1929.
5. Hamilton, W. F., Riley, R. L., Attyah, A. M., Cournand, A., Fowell, D. M., Himmelstein, A., Noble, R. P., Remington, J. W., Richards, D. W., Jr., Wheeler, N. C. and Witham, A. C. Comparison of the Fick and dye injection methods of measuring the cardiac output in man. *Am. J. Physiol.*, 153: 309, 1948.
6. Hetzel, P. S., Swan, H. J. C. and Wood, E. H. Influence of injection site on arterial dilution curves of T-1824, *J. Appl. Physiol.*, 7: 66, 1954.
7. Lawson, H. C., Shadle, O. W., Coleman, E. S. and Holtgrave, D. E. A comparison of intracardiac and intravenous injections for the measurement of cardiac output by the dilution technique. *Circulation Res.*, 2: 251, 1954.
8. Gregersen, M. I. Practical method for the determination of blood volume with the dye T-1824. *J. Lab. & Clin. Med.*, 29: 1266, 1944.
9. Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R. and Sawyer, C. G. Effect of exercise on circulatory dynamics of normal individuals. *J. Appl. Physiol.*, 3: 439, 1951.
10. Edholm, O. G. and Howarth, S. Studies on the peripheral circulation in osteitis deformans. *Clin. Sc.*, 12: 277, 1953.
11. Epstein, F. H., Shadle, O. W., Ferguson, T. B. and McDowell, M. E. Cardiac output and intracardiac pressures in patients with arterio-venous fistulas. *J. Clin. Investigation*, 32: 543, 1953.
12. Lequime, J., Denolin, H. and Verniory, A. La circulation au cours de la maladie de Paget. *Acta cardiol.*, 7: 319, 1952.
13. Lequime, J. and Denolin, H. Circulatory dynamics in osteitis deformans. *Circulation*, 12: 215, 1955.
14. Bazett, H. C. A consideration of the venous circulation in factors regulating blood pressure, p. 53. Tr. Third Conf. Josiah Macy, Jr. Foundation, 1949.
15. Kay, H. D., Levy-Simpson, S., Riddoch, G. and Vilvandre, G. E. Osteitis deformans. *Arch. Int. Med.*, 53: 208, 1934.
16. Sornberger, C. F. and Smedal, M. I. The mechanism and incidence of cardiovascular changes in Paget's disease (osteitis deformans). *Circulation*, 6: 711, 1952.
17. Warren, J. V., Elkin, D. C. and Nickerson, J. L. The blood volume in patients with arteriovenous fistulas. *J. Clin. Investigation*, 30: 220, 1951.
18. Sjöstrand, T. Volume and distribution of blood and their significance in regulating the circulation. *Physiol. Rev.*, 33: 202, 1953.
19. Walser, M., Seldin, D. W. and Burnett, C. H. Blood volume and extracellular fluid volume during administration of ACTH and cortisone. *Am. J. Med.*, 18: 454, 1955.
20. Perera, G. A., Fleming, T. C., Pines, K. L. and Crymble, M. Cortisone in hypertensive vascular disease. *J. Clin. Investigation*, 29: 739, 1950.
21. Horowitz, O., Sayen, A., Naide, M. amd Hollander, J. L. Measurements of certain cardiovascular responses to ACTH and cortisone in man. *Am. J. M. Sc.*, 221: 669, 1951.

Essential Hyperlipemia*

Report of Four Cases, with Special Reference to Abdominal Crises

LEO J. CORAZZA, M.D. *and* RALPH M. MYERSON, M.D.
Philadelphia, Pennsylvania

HYPERLIPEMIA is a clinical state characterized by an increase in the neutral fat fraction of the blood lipids. When this increase is of sufficient degree, the serum has a grossly milky or chylous appearance.

Three types of hyperlipemia are recognized. Alimentary hyperlipemia is a physiologic phenomenon, the neutral fat content of the blood reaching a peak four to six hours after ingestion of a fat-rich meal. It is unaccompanied by an increase in serum cholesterol or phospholipids. Secondary hyperlipemia has been described in diabetes mellitus, the nephrotic stage of chronic glomerulonephritis, pancreatitis, myxedema, starvation, von Gierke's disease, Niemann-Pick disease, amyloidosis, renal vein thrombosis and toxic hepatoses. In essential hyperlipemia there is no apparent cause for the hyperlipemia. A familial tendency has been noted and a genetic factor postulated. The experiments of Thannhauser and Stanley with iodine-labelled fat suggest that defective removal of fat from the blood is an important factor in patients with essential hyperlipemia. They found that the disappearance of the labelled fat was considerably prolonged in such patients as compared with normal individuals.[1] In essential hyperlipemia there is often a concomitant but less marked rise in serum cholesterol and phospholipid concentration. Ultracentrifugal lipoprotein patterns show characteristic marked elevations of the low-density lipoprotein classes.[2] Transient glycosuria and elevations of the blood sugar levels have been described.

Approximately sixty-five cases of essential hyperlipemia have been recorded;[3–8] males have predominated. To date the disorder has been reported in only two Negroes.[9,10] It may occur at all ages, from infancy to old age.

Clinically, essential hyperlipemia is characterized typically by recurrent abdominal pain, hepatosplenomegaly, cutaneous xanthomatosis and lipemia retinalis. Secondary hypersplenism, relieved by splenectomy, has been reported in one case.[11] Any or all of the typical manifestations may be absent. The diagnosis is frequently made by the accidental discovery of a milky serum.

Abdominal pain has been a prominent complaint in over half of the reported cases. The pain varies considerably in severity, location and frequency. It may be accompanied by fever, leukocytosis and increased sedimentation rate. In three of four cases of essential hyperlipemia observed by the authors, abdominal pain was a presenting complaint and the findings closely simulated those of an acute surgical emergency.

CASE REPORTS

CASE 1. C. C., a thirty-nine year old Negro man, was admitted to the Veterans Administration Hospital, Philadelphia, on March 11, 1954, with the chief complaints of abdominal pain, nausea and vomiting. The patient gave a history of recurrent attacks of abdominal pain since childhood and had been hospitalized repeatedly. The pain was epigastric, severe, and seemed to be precipitated by overeating. On at least two previous hospitalizations lipemic serum, transient glycosuria and hyperglycemia had been noted. The diagnosis of chronic relapsing pancreatitis had been made but at no time had there been any elevation of urinary diastase or increased serum levels of lipase or amylase. The past history was non-contributory and the family history was not remarkable.

Physical examination revealed moderate epigastric tenderness and spasm. The liver and spleen were not palpable. The skin was clear. Temperature, pulse and blood pressure were within normal limits.

Laboratory studies revealed an initial leukocyte count of 24,000 per cu. mm. with 74 per cent neutrophils, 10 per cent juvenile neutrophils and 16 per cent lymphocytes; the hemoglobin was 11.5 gm. per 100 ml. and the hematocrit 32 per cent. Moderate glycosuria was present. The serum was consistently

* From the Medical Service, Veterans Administration Hospital, Philadelphia, Pennsylvania.

TABLE 1

SERUM LIPID STUDIES

		CHOLESTEROL			PHOSPHO-LIPIDS	FATTY ACIDS Mg/100 ml.				NEUT. FAT	TOTAL LIPIDS	LIPEMIA	REMARKS
		Total Mg/100 ml.	Esters Mg/100 ml.	Ester/Total %	Mg/100 ml.	Total	Chol. Esters	Phospho-lipids	Neut. fat	Mg/100 ml.	Mg/100 ml.	0 to ++++	
Normal Values		150-250	100-170	67	150-250	260 625	65-115	100-170	80 350	85-365	520 920	0	
PATIENT	DATE												
C.C.	3-26-54	1202	723	60	600	1623	482	400	741	780	3064	++++	
	4-6-54	839	488	58	480	820	325	320	175	184	1828	++	LFD* -11 Days
	12-28-55	180	120	67							620	0	LFD* -21 Months
M.K.	12-13-55	450	360	80	470	1229	240	313	676	712	1872	+++	
	2-6-56	317	102	32	355	540	68	238	234	246	986	0	LFD* -55 Days
	3-30-56	318	152	48	349	490	101	233	156	164	932	0	LFD* -108 Days
C.P.	2-6-56	1040	348	34	1124	5130	232	750	4148	4360	6856	++++	
	3-26-56	677	434	64	447	964	290	298	376	398	1812	++	LFD* -6 Days
	4-17-56	375	198	53	390	801	132	260	409	430	1327	++	LFD* -28 Days
A.S.	2-25-49	347	235	68	335	2106	157	257	1692	1781	2620	++++	

*Low Fat Diet

milky. The blood sugar was 238 mg. per 100 ml. Blood urea nitrogen, CO_2 combining power, sodium, potassium and chloride were within normal limits. The serum amylase was 78 units, serum lipase 0.3 units. Tests of renal and hepatic function were normal. There was no evidence of porphyria. Sickle cell preparations were negative. Serum lipid studies are shown in Table 1. Roentgenographic studies of the chest, gall bladder and upper gastrointestinal tract, and an intravenous urogram were within normal limits. There was no evidence of calcification of the pancreas. A biopsy of the liver was reported as within normal limits.

The patient was given a diet containing 20 gm. of fat. Glycosuria disappeared promptly, although a diabetic glucose tolerance curve remained. (Fig. 1.) There was a perceptible decrease in serum turbidity, and serum lipid studies eleven days after initiation of the low fat regimen showed a marked decrease in all components. The patient has been followed twenty-one months and has had no further episodes of abdominal distress since the low fat diet was instituted.

GLUCOSE TOLERANCE TESTS
of four essential hyperlipemia patients

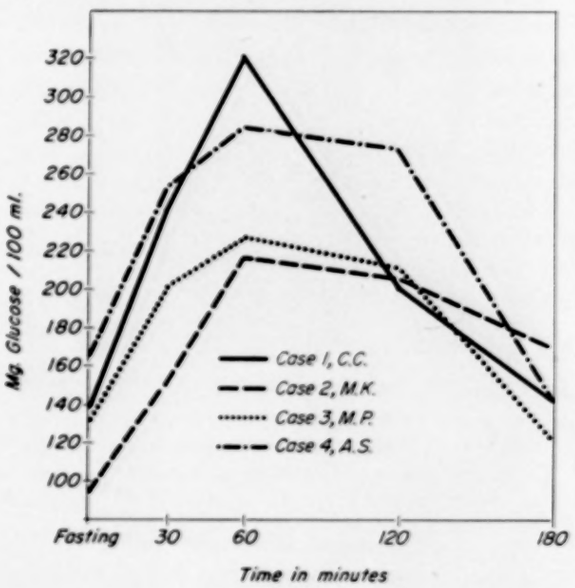


FIG. 1.

CASE II. M. K., a thirty-eight year old white man, was admitted to the Philadelphia Veterans Administration Hospital on December 12, 1955, with a chief complaint of abdominal pain and vomiting of one day's duration. The patient had experienced recurrent bouts of abdominal pain since 1943. The pain was described as generalized but most severe in the left upper quadrant and usually accompanied by vomiting. In 1952 and 1953 exploratory laparotomies had been performed but no definite abnormality was found. The pancreas was described as grossly "fibrotic" at the time of the second operation. Following the first operation the patient experienced a typical attack of gout involving the first metatarsophalangeal joints and accompanied by an elevation of the serum uric acid level. The presenting episode of abdominal pain began the day prior to admission and was accompanied by severe vomiting and a grand mal convulsion. There was no history of gastrointestinal bleeding and there were no symptoms referable to the genitourinary tract. The family history was negative.

Physical examination revealed a well developed and nourished young adult white man who appeared to be in acute distress. His temperature was 99.4°F., pulse 88 per minute and blood pressure 140/100. The posi-

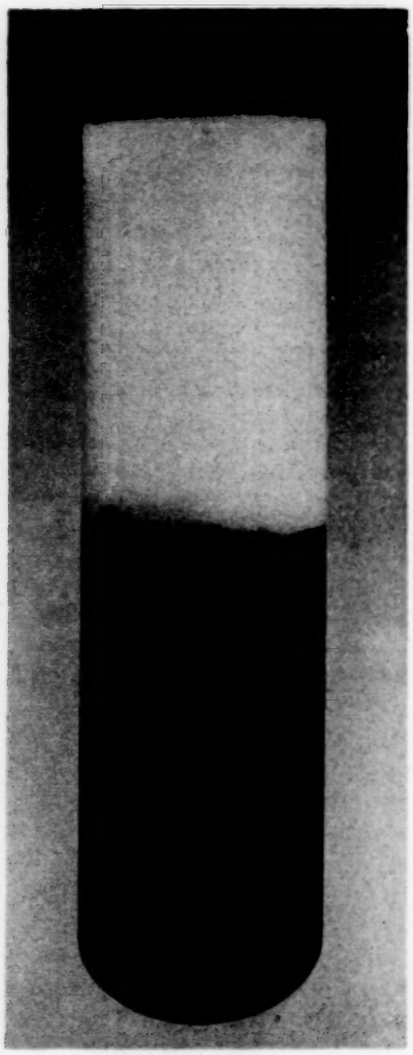


FIG. 2. Case III. Milky appearance of patient's serum.

tive physical findings were confined to the abdomen. There were two well healed surgical scars. Tenderness was present in the left upper quadrant and left flank. There was no spasm or rebound tenderness and no organs were palpable.

Laboratory studies on admission revealed a normal hemogram and urinalysis. The serum had a milky appearance during the first five days of hospitalization. The results of serum lipid studies are shown in Table I. Serum amylase and lipase studies were within normal limits. The serum uric acid was 6.5 mg. per 100 ml. Tests of renal and hepatic function and a spinal fluid examination were within normal limits. A glucose tolerance test performed eleven days after admission revealed a diabetic type of curve. (Fig. 1.) No glycosuria was present. An electroencephalogram and electrocardiogram revealed no abnormalities. Roentgenographic studies of the chest, abdomen, upper gastrointestinal tract, gall bladder and skull, and an intravenous urogram were within normal limits.

The patient was placed on a low fat regimen, his symptoms subsided promptly and have not recurred on this program. Six weeks after initiation of a low fat diet the patient's serum was clear and the blood lipid concentrations were at the upper limits of normal. (Table I.)

CASE III. M. P., a forty-six year old white man, was admitted to the Veterans Administration Hospital, Philadelphia on December 15, 1955, with the chief complaints of abdominal pain, nausea and vomiting of three months' duration. Initially, the symptoms were intermittent and occurred only in the morning. The pain gradually increased in frequency, duration and severity, and three days prior to admission became continuous and very severe. The pain was generalized and did not radiate. The past history and family history were not significant.

Physical examination revealed a moderately obese man who appeared acutely ill. There was diffuse abdominal tenderness, but no spasm or rebound tenderness. Peristalsis appeared to be normal. The liver and spleen could not be felt. The remainder of the examination was within normal limits. Funduscopic examination was negative; the skin was clear.

Laboratory studies revealed a normal hemogram. The serum was persistently milky in appearance. (Fig. 2.) Urinalysis, fasting blood sugar, blood urea nitrogen, serologic tests and liver function studies were within normal limits. Roentgenographic studies of the chest, gall bladder and upper gastrointestinal tract, and an electrocardiogram were not remarkable. Blood lipid studies are listed in Table I. A diabetic type of glucose tolerance test was present but there was no glycosuria. (Fig. 1.)

Following institution of a low fat diet his symptoms improved and within the next few weeks there was a perceptible decrease in the turbidity of the patient's serum. Repeat lipid studies showed a marked decrease in all fractions. (Fig. 1.) A biopsy of the liver showed a moderate amount of fatty infiltration. No lipoidal cells could be seen. The patient has remained essentially asymptomatic on a low fat intake. Attempts to provoke an attack with a high fat diet have been unsuccessful.

CASE IV. A. S., a twenty-eight year old white man, was admitted to the Veterans Administration Hospital, Wilmington on January 27, 1949. He gave a history of recurrent attacks of acute low back pain radiating down both legs. One year prior to admission the patient was told he had a "little sugar in his urine." The past history was otherwise negative and the family history was not remarkable.

Physical examination was within normal limits. The liver and spleen were not enlarged and the skin was clear. The hemogram, urinalysis and tests of renal and

hepatic function were within normal limits. Lipemic serum was present on all occasions. The results of serum lipid partitions are shown on Table 1. Roentgenograms of the chest, cholecystogram, intravenous urogram and electrocardiogram were within normal limits. The results of a glucose tolerance test are shown in Figure 1. The patient was given a diet containing 20 gm. of fat and has remained asymptomatic. No follow-up studies have been obtained.

COMMENTS

The cause of abdominal pain in essential hyperlipemia is obscure. Sudden enlargement of the liver and spleen coincident with an abdominal crisis occurred in an eleven year old female patient studied by Holt and his associates.[12] Attacks occurred when the serum lipid level reached or exceeded "eight per cent," and it was postulated that sudden accumulation of fat in the liver and spleen produced engorgement and pain. This patient has been followed for nineteen years and has continued to have numerous attacks of abdominal pain. Unlike the episodes occurring during childhood, the attacks in adults have not been preceded by a rise in serum lipids or accompanied by enlargement of the liver and spleen. Others have noted that hepatosplenomegaly is less frequent in adults with essential hyperlipemia than in children.[5,14] Hepatosplenomegaly was absent in the four patients presented.

There are striking similarities between the abdominal crisis of essential hyperlipemia and the syndrome of relapsing pancreatitis. The observations of Poulsen[15] and the extensive studies of Klatskin and Gordon[4] indicate that when relapsing pancreatitis and essential hyperlipemia occur together, pancreatitis is the result rather than the cause of hyperlipemia. Further evidence of this relationship is presented in other cases of pancreatitis and essential hyperlipemia in which xanthomatosis has appeared before the onset of abdominal pain.[16–20]

It is possible, but unlikely, that hyperlipemia may produce abdominal pain by producing xanthomatous or atherosclerotic lesions in the pancreas and other viscera. Klatskin and Gordon suggested that the abdominal crisis of essential hyperlipemia may be due to embolization of agglutinated serum lipid particles of the pancreas and liver.[4] The epileptiform seizure experienced by patient M. K. suggests the possibility of a similar cerebral process. Transient neurologic findings have been described in other cases.[15,21] Direct proof of any mechanism for the production of pain is lacking. Not all patients with essential hyperlipemia develop abdominal pain, as in the case of patient A. S., and in those patients with pancreatitis there may be long symptom-free periods despite the persistence of hyperlipemia.

Tissue studies have been limited. Biopsies of liver and bone marrow have demonstrated lipoid-containing cells in some cases.[7,22–24] Chapman and Kinney reported the postmortem findings in a twenty-one month old infant with essential hyperlipemia.[25] Many fat-containing cells were scattered throughout the spleen, marrow and lymph nodes. The liver, pancreas and other viscera were normal. As far as can be determined, an abdominal crisis prior to death did not occur in this infant. In patients with essential hyperlipemia without pancreatitis, exploratory laparotomy has been essentially negative.[5,20] Chylous ascites and a retroperitoneal mass were found in Holt's patient but the pancreas is said to have been normal.[12]

It has been shown by many observers that a low fat diet can control, to some extent at least, the degree of hyperlipemia and the abdominal crises. A rapid decrease in the lipoidal cells in the liver and bone marrow has been produced by such a diet.[24] Intravenous heparin usually produces a prompt and perceptible decrease in serum turbidity in essential hyperlipemia and an absolute decrease in fat content. A shift toward lipoproteins of higher density has been reported.[3–5,26–29] Recently Hollister and Kanter reported similar results with chlorpromazine, possibly mediated by its adrenolytic activity.[29] Their patient remained free of pain during periods of heparin or chlorpromazine administration and relapsed when given a placebo.

Klatskin and Gordon reported that the administration of corticotropin to a patient during a period of fat restriction resulted in a marked increase in the turbidity of the serum without, however, provoking abdominal pain.[4] There was a relatively small increase in the total fatty acid content of the blood, suggesting that corticotropin may have produced turbidity by altering the physical state of the serum lipids. A similar suggestion has been made by Adlersberg and his associates.[30] Rich and his co-workers noticed a rise in serum lipids and the development of milky serum in rabbits given cortisone.[31]

Seifter and Baeder have recently isolated a lipid-mobilizing factor from a dialysate of human and animal plasma. Injections of this

lipid-mobilizing factor in animals resulted in mobilization of body fat with consequent marked increase in plasma lipids.[32] Steiger and his associates administered to human subjects a lipid-mobilizing factor, prepared from the plasma of cortisone-treated horses, and confirmed its potent hyperlipemic effect. In human patients the lipid-mobilizing factor caused an increase in the serum cholesterol, phospholipids and neutral fats, a pattern similar to the one usually seen in essential hyperlipemia. No toxic effects or abdominal pain were noted in any patients.[33]

The observations made on essential hyperlipemia suggest that it may be the result of (1) a basic defect in the normal lipemia-clearing mechanism, (2) a constitutional overresponsiveness of the fat depots to the normal fat-mobilizing stimuli, or (3) the presence of an abnormal fat-mobilizing stimulus.

SUMMARY

Four cases of essential hyperlipemia have been presented. In three of the four patients the presenting complaint was severe abdominal pain, suggesting the presence of a surgical emergency.

Serum lipid partition studies revealed a marked increase in all of the lipid constituents, especially neutral fat. Three of the four patients who have been followed have demonstrated improvement on a low fat regimen. All four patients have moderate impairment of glucose tolerance.

The mechanisms responsible for essential hyperlipemia and the production of abdominal pain in this disorder have been discussed.

REFERENCES

1. Thannhauser, S. J. and Stanley, M. M. Serum fat curves following administration of I_{131} labeled neutral fat to normal subjects and those with idiopathic hyperlipemia. *Tr. A. Am. Physicians*, 62: 245, 1949.
2. Gofman, J. W., Rubin, L., McGinley, J. P. and Jones, H. B. Hyperlipoproteinemia. *Am. J. Med.*, 17: 514, 1954.
3. Lever, W. F., Smith, P. A. and Hurley, N. A. Idiopathic hyperlipemia and primary hypercholesteremic xanthomatosis. I. Clinical data and analysis of the plasma lipids. *J. Invest. Dermat.*, 22: 33, 1954; II. Analysis of the plasma proteins and lipids by means of electrophoresis and fractionation of the plasma proteins; effect of high speed centrifugation and of extraction with ether on the plasma proteins and lipids. *Ibid.*, 22: 53, 1954; III. Effects of intravenously administered heparin on the plasma proteins and lipids. *Ibid.*, 22: 71, 1954; Discussion. *Ibid.*, 22: 84, 1954.
4. Klatskin, G. and Gordon, M. Relationship between relapsing pancreatitis and essential hyperlipemia. *Am. J. Med.*, 12: 3, 1952.
5. Joyner, C. R., Jr. Essential hyperlipemia. *Ann. Int. Med.*, 38: 759, 1953.
6. Malmros, H., Swahn, B. and Truedsson, E. Essential hyperlipemia. *Acta med. Scandinav.*, 149: 91, 1954.
7. Movitt, E. R., Gerstl, B., Sherwood, F. and Epstein, C. C. Essential hyperlipemia. *Arch. Int. Med.*, 87: 79, 1951.
8. Joske, R. A. Essential hyperlipemia. *M. J. Australia*, 1: 826, 1955.
9. Oberman, J. L. and Fankhouser, R. L. Idiopathic periodic (familial) hyperlipemia. *Bull. New York M. Coll.*, 15: 121, 1952.
10. Fulton, J. K. Essential lipemia, acute gout, peripheral neuritis and myocardial disease in a Negro man; response to corticotropin. *Arch. Int. Med.*, 89: 303, 1952.
11. Berk, M. Secondary hypersplenism with recurrent gastrointestimal bleeding. *California Med.*, 78: 518, 1953.
12. Holt, L. E., Jr., Aylward, F. X. and Timbres, H. G. Idiopathic familial lipemia. *Bull. Johns Hopkins Hosp.*, 64: 279, 1939.
13. Ahrens, E. H., Jr. In: Essential Hyperlipemia in Fat Metabolism: A Symposium on the Clinical and Biochemical Aspects of Fat Utilization in Health and Disease, p. 61. Edited by V. A. Najjar. Baltimore, 1954. Johns Hopkins Press.
14. Thannhauser, S. J. Lipidosis: Diseases of the Cellular Lipid Metabolism. New York, 1950. Oxford University Press.
15. Poulsen, H. M. Familial lipemia, a new form of lipidosis showing increase in neutral fats combined with attacks of acute pancreatitis. *Acta med. Scandinav.*, 138: 413, 1950.
16. Wijnhausen, O. J. Ueber Xanthomatose in einem Falle rezidivierende Pankreatitis. *Klin. Wchnschr.*, 58: 1268, 1921.
17. Collett, R. W. and Kennedy, R. L. J. Chronic relapsing pancreatitis associated with hyperlipemia in an eight year old boy. *Proc. Staff Meet., Mayo Clin.*, 23: 158, 1948.
18. Bernstein, S. S., Williams, H. H., Hummel, F. C., Shepherd, M. L. and Erickson, B. N. Metabolic observations on a child with essential hyperlipemia. *J. Pediat.*, 14: 570, 1939.
19. Hopgood, W. C. Idiopathic hyperlipemia. *New England J. Med.*, 238: 429, 1948.
20. Bloomfield, A. L. and Shenson, B. The syndrome of idiopathic hyperlipemia with crises of violent abdominal pain. *Stanford M. Bull.*, 5: 183, 1947.
21. Jöel, E. Zur Klinik der Lipämie. *Ztschr. f. klin. Med.*, 100: 46, 1924.
22. Koszalka, M. F. and Levin, J. J. Idiopathic hyperlipemia. *Ann. Int. Med.*, 33: 473, 1950.
23. Shore, S. C. and Schrire, V. A possible case of idiopathic hyperlipemia. *Clin. Proc.*, 6: 138, 1947.
24. Bruton, O. C. and Kanter, A. J. Idiopathic familial hyperlipemia. *Am. J. Dis. Child.*, 82: 153, 1951.
25. Chapman, F. D. and Kinney, T. D. Hyperlipemia;

"idiopathic lipemia." *Am. J. Dis. Child.*, 62: 1014, 1941.

26. Soffer, A. Office diagnosis and treatment of essential hyperlipemia. *Postgrad. Med.*, 18: 83, 1955.
27. Herzstein, J., Chun-I Wang and Adlersberg, D. Effect of heparin on plasma lipid partition in man: studies in normal persons and in patients with coronary atherosclerosis, nephrosis and primary hyperlipemia. *Ann. Int. Med.*, 40: 290, 1954.
28. Van Eck, W. F., Peters, J. P. and Man, E. M. Significance of lactescence in blood serum. *Metabolism*, 1: 383, 1952.
29. Hollister, L. E. and Kanter, S. L. Essential hyperlipemia treated with heparin and chlorpromazine. *Gastroenterology*, 29: 1069, 1955.
30. Adlersberg, D., Schaefer, L. E. and Drachman, S. R. Studies on hormonal control of serum lipid partition in man. *J. Clin. Endocrinol.*, 11: 67, 1951.
31. Rich, A. R., Cochran, T. H. and McGoon, D. C. Marked lipemia resulting from the administration of cortisone. *Bull. Johns Hopikns Hosp.*, 88: 101, 1951.
32. Seifter, J. and Baeder, D. H. Occurrence in plasma of an extractable lipid mobilizer (LM). *Proc. Soc. Exper. Biol. & Med.*, 91: 42, 1956.
33. Steiger, W. A., Zarafonetis, C. J. D., Baeder, D. H. and Seifter, J. Preliminary observations in man on a lipid mobilizing plasma dialysate. Presented at the Eastern Pennsylvania Regional Meeting, American College of Physicians, Philadelphia, 1956.

Review

The Use of ACTH, Cortisone, Hydrocortisone and Related Compounds in the Management of Ulcerative Colitis*

Experience in 180 Patients

JOSEPH B. KIRSNER, M.D., MANUEL SKLAR, M.D.† *and* WALTER L. PALMER, M.D.

Chicago, Illinois

THE role of corticotropin, cortisone and related compounds in the treatment of ulcerative colitis has been studied frequently in the past five years; the literature, comprising chiefly case reports and small groups of patients, has been reviewed elsewhere [*1*]. Our experience with ACTH and adrenal steroids dates to January 1950; early results, recorded in 1951 [*2*] and 1954 [*1*], indicated a generally beneficial response. Truelove and Witts [*3*] and Maltby et al. [*4*] also have published favorable studies recently. The present paper, summarizing observations on the course of 180 patients with ulcerative colitis treated with ACTH, cortisone, hydrocortisone, prednisone and prednisolone during a period of six years, presents further evidence that these compounds are useful adjuncts in the management of this serious disease.

PATIENTS STUDIED

General Observations. The series includes ninety-three men and eighty-seven women. The majority were between the ages of twenty and forty. The duration of symptoms ranged from one month to thirty years; it was less than twelve months in fifty-three patients; one to five years in fifty-five; five to fifteen in fifty-four; fifteen to twenty years in eleven; and more than twenty years in seven individuals. Frequent and prolonged hospitalization had been necessary in many cases; colectomy and ileostomy had been recommended elsewhere in at least forty-four patients. The colon was examined radiologically in 165 patients; the entire colon was involved in sixty-eight; varying portions of the bowel were affected in sixty-eight; the colon appeared normal by x-ray in twenty-nine persons (Table I); characteristic proctoscopic changes were noted in the latter group. Moderately severe or severe inflammation of the bowel wall, with edema, granularity, friability and bloody fluid in the rectum was observed at proctoscopy in 147 patients (Table II); characteristic roentgen evidence of the disease proximal to the rectosigmoid was noted in thirty-three individuals with minimal or no change proctoscopically. Complications, frequently multiple, developed in 128 patients. (Table III). The severity of the colitis was classified as mild in fourteen patients, moderately severe in eighty-three and severe in eighty-three persons. Emotional difficulties, often severe and complicated, were recognized in most patients.

Previous Laboratory Findings: The feces consistently were negative for pathogenic bacteria and parasites. X-rays of the chest were normal. In the patients tested the following procedures

* From the Department of Medicine, University of Chicago, Chicago, Illinois. This study was supported in part by the Wallach Fund for Gastrointestinal Research (University of Chicago). The corticotropin was provided generously by the Wilson Company, Chicago, Ill.; cortisone by Merck and Co., Rahway, N. J.; hydrocortisone by the Upjohn Co., Kalamazoo, Mich.; and prednisone and prednisolone by the Schering Corp., Bloomfield, N. J. It was presented in part at the Pan American Congress of Gastroenterology, Havana, Cuba, January 1956.

† United States Public Health Service Research Fellow, National Cancer Institute.

also were negative: skin tests for lymphopathia venereum, histoplasmosis and coccidiodomycosis, serum agglutinins against enteric pathogens, oral glucose tolerance test, serum calcium and phosphorus, basal metabolism, gastric secretion and tests for L. E. cells. The total plasma proteins were reduced in thirty-two patients; however, the values for plasma globulin not infrequently were elevated.

TABLE I
EXTENT OF ULCERATIVE COLITIS (RADIOLOGIC)

X-Ray Extent	Clinical Severity			Total Patients
	Mild	Moderate	Severe	
Entire colon	0	23	45	68
Left colon	4	18	10	32
Left and transverse colon	0	10	7	17
Segmental	3	6	2	11
Enterocolitis	0	1	7	8
Normal	6	19	4	29
Not examined	1	6	8	15
Total patients	14	83	83	180

TABLE II
SEVERITY OF ULCERATIVE COLITIS (PROCTOSCOPIC)

Proctoscopic Findings	Clinical Severity			Total Patients
	Mild	Moderate	Severe	
Severe	0	28	45	73
Moderate	6	40	28	74
Mild	8	11	5	24
Normal	0	4	5	9
Total patients	14	83	83	180

METHOD OF STUDY

The method of study was the same as that employed in the first forty patients [2], except for the omission of placebo controls; fecal outputs were not recorded and eosinophil counts were not made routinely. All patients, except for those few with new, fulminant disease, had been under prolonged observation and the previous course of their illness was known. The response to medical treatment had been unsatisfactory or the disease had recurred after earlier improvement. The original forty patients received ACTH or cortisone in addition to a bland diet and occasionally sedatives. Treatment in the remaining 140 patients also included antispasmodics, vitamins, opiates when necessary, and sulfonamides, usually sulfaguanidine 8.0 gm. per day; sulfathalidine® and azulfidine 4.0 to 6.0 gm., sulfadiazine and gantrisin® 2.0 to 4.0 gm.

TABLE III
COMPLICATIONS PRIOR TO ACTH OR STEROID THERAPY—128 PATIENTS (52 WITHOUT COMPLICATIONS)

Anemia, hemorrhage	68
Arthritis	40
Polyps	35
Hypoproteinemia	32
Rectal fistula or abscess	18
Thrombophlebitis	12
Rectal stricture	8
Erythema nodosum	7
Iritis, iridocyclitis	7
Pyoderma	5
Perforation	2
Carcinoma	1

daily, also were prescribed in some instances. Penicillin and streptomycin were administered to patients with fever and toxemia or with clinical evidence suggesting pericolitis. The intake of salt was limited chiefly in those patients receiving large doses of ACTH; mercurial diuretics were administered occasionally. Potassium salts were not prescribed routinely because of their tendency to increase diarrhea but were administered in selected cases, preferably intravenously. Therapy usually was instituted in the hospital; a few individuals were treated in the outpatient department only.

Corticotropin, aqueous, the drug of choice in most instances, was prescribed initially in doses of 30 units intramuscularly every six hours. In critical situations the corticotropin was administered intravenously in 5 per cent dextrose and water in quantities of 20 to 40 units over a twenty-four-hour period. ACTH gel was utilized exclusively as maintenance therapy. Hydrocortisone was prescribed initially in quantities of 200 mg. daily by mouth in four divided doses; the intravenous dosage was 100 mg. per twenty-four hours. Cortisone was administered orally in total daily amounts of 200 to 300 mg. Our early experience with prednisone and prednisolone was limited and initial daily doses were only 20 to 40 mg.; subsequently, the effective dose was established as 60 to 100 mg.; there appeared to be no differences between the two compounds and they are discussed as one.

With subsidence of symptoms, dosages were reduced by decrements of 10 to 25 per cent, at intervals of one to two weeks during hospitalization and later every three to six weeks or longer, depending upon the

individual response. Many patients, treated initially with ACTH, were transferred, as the time of discharge from the hospital approached, to oral steroids, and the corticotropin was withdrawn gradually.

ACTH was prescribed in 145 patients; in fifty-nine it was the only corticoid employed; hydrocortisone was given to seventy-five patients and in twenty was the lone steroid; cortisone was administered in fifty-five patients and in six was used alone. Prednisone and prednisolone were prescribed in twenty-two patients; all except one had received other corticoids. The total dosages and duration of therapy are summarized in Tables IV and V.

TABLE IV
TOTAL DURATION OF ACTH OR STEROID THERAPY IN INDIVIDUAL PATIENTS

Months	ACTH	Hydrocortisone	Cortisone	Prednisolone, Prednisone
<4	104	30	28	19
4–8	27	27	9	3
8–12	4	12	6	0
12–24	6	6	7	0
24–36	3	0	4	0
36–48	1	0	1	0
Total patients	145	75	55	22

TABLE V
TOTAL AMOUNTS OF ACTH AND ADRENAL STEROIDS IN INDIVIDUAL PATIENTS

1,000 Units	ACTH	Grams	Hydrocortisone	Cortisone	Prednisone Prednisolone
<5	93	<5	17	20	21
5–15	39	5–15	34	18	1
15–30	8	15–30	20	12	0
30–60	3	30–60	4	4	0
60–100	2	60–100	0	1	0
Total patients	145	.....	75	55	22

RESULTS

Initial Results. The initial clinical response to ACTH was judged as good in ninety-three patients, moderately favorable in twenty-six and slight or nil in fifteen; thus, 119 of the 134 patients treated initially with ACTH improved significantly during treatment. (Table VI.) The beneficial effect was characterized by prompt disappearance of fever, tachycardia, abdominal distress and blood in the feces; more gradual improvement in the consistency of the stools and reduction in number of bowel movements; increase in appetite and a sense of well being. There was no absolute correlation chronologically or in degree between the emotional upsurge and the status of the colitis; some patients not responding clinically also reported a sense of well-being. The proctoscopic appearance of the bowel improved significantly in the majority of

TABLE VI
RESPONSE DURING INITIAL COURSE OF ACTH OR STEROID THERAPY

Steroid	Response	Total Patients	Per cent
ACTH	Good	93	70
	Moderate	26	19
	Slight or nil	15	11
Cortisone	Good	5	36
	Moderate	5	36
	Slight or nil	4	28
Hydrocortisone	Good	14	48
	Moderate	10	33
	Slight or nil	5	19
Prednisone, Prednisolone	Good	0	..
	Moderate	1	33
	Slight or nil	2	67

TABLE VII
RESPONSE DURING INITIAL COURSE OF ACTH OR STEROID THERAPY—OVER-ALL RESULTS

Response	Clinical Severity			Total Patients	Per cent
	Mild	Moderate	Severe		
Good.....	12	48	52	112	62
Moderate...	1	25	16	42	23
Slight or nil	1	10	15	26*	15
Total patients..	14	83	83	180	..

* Of this group ten patients later responded favorably to aqueous corticotropin.

patients, but more slowly than the symptoms. The response to hydrocortisone and cortisone was satisfactory in the majority of patients treated (Table VI) but the effects were less striking and more gradual than those observed with ACTH; hydrocortisone was more effective than cortisone. Of the twenty-six patients not responding to initial therapy with ACTH gel, hydrocortisone or cortisone, ten improved significantly when given aqueous corticotropin; hence these ten are grouped with the 154 patients initially responding favorably, a total of 164 favorable responses. Prednisone and prednisolone initially were prescribed in relatively small amounts in three patients, with disappointing results. Subsequently, fifteen other patients, each of whom had received corticotherapy previously, were treated effectively with larger amounts (60 to 100 mg.). As might be expected, the trend of the response to therapy suggests slightly more favorable results in patients with mild or moderate disease than in the instances of severe ulcerative colitis. (Table VII.)

TABLE VIII
RESPONSE DURING SUBSEQUENT COURSES OF ACTH OR STEROID THERAPY
(148 COURSES IN 91 PATIENTS)

Steroid	Response	Total Patients
ACTH	Good	33
	Moderate	22
	Slight or nil	13
Cortisone	Good	6
	Moderate	14
	Slight or nil	6
Hydrocortisone	Good	16
	Moderate	21
	Slight or nil	8
Prednisone, Prednisolone	Good	4
	Moderate	3
	Slight or nil	2
Over-all response	Good	59 (40%)
	Moderate	60 (41%)
	Slight or nil	29 (19%)

TABLE IX
DURATION OF OBSERVATION AFTER TERMINATIGN OF STEROID THERAPY
(To October 1, 1955)

Months	Patients
<12	41
12–24	22
24–36	16
36–48	19
48–60	16
>60	8
Total patients	122

TABLE X
DURATION OF CONTINUING MAINTENANCE THERAPY
(To October 1, 1955)

Months	Patients
<3	9
3–6	12
6–12	14
12–24	5
24–36	7
36–48	1
Total patients	48

Recurrences in ninety-one patients required 148 repeated courses of corticoid therapy. Although the immediate response usually was satisfactory, the improvement tended to be less striking than that accompanying the first course of therapy; thus, "good results" decreased from 62 per cent during initial courses of therapy to 40 per cent in subsequent courses. (Table VIII.)

Late Results. The period of observation after completion of therapy ranges from one to sixty-seven months. Forty-one patients have been followed up less than one year; twenty-two for one to two years; and fifty-nine for more than two years (Table IX); forty-eight patients continue therapy. (Table X.) Of the 164 patients responding satisfactorily, ninety-two have experienced recurrences thus far; thirty-two occurred within the first three months; in fact, twelve patients experienced an immediate exacerbation, suggesting premature withdrawal of the drug. In another thirty-two patients, symptoms returned within a year, and in the remaining twenty-eight, at intervals up to five years. (Table XI.) Relapses during maintenance therapy in twenty-three patients usually occurred at relatively low dosage levels, implying persistent active colitis suppressed by a high steroid level, with clinical escape when the concentration of steroids decreased below the

necessary threshold. (Table XII.) Of the 164 patients responding to ACTH, cortisone, hydrocortisone and the newer analogues, initially or during subsequent courses, 115 (70 per cent) experienced recurrences. Of these recurrences or relapses, seventy-five subsided when retreated with corticoids; twenty-four underwent remission with conventional medical therapy; active disease has persisted in nine cases despite all forms of medical treatment; five required operations and two died. (Table XIII.) Multiple recurrences, totalling sixty in number, have been observed in forty-six patients; many improved during succeeding courses of corticotherapy but the degree of responsiveness frequently diminished.

Remissions have continued in twenty-seven patients since their first successful course of corticoids; nineteen of these have remained well for a year or more. Nine additional patients have been in remission since a second course of therapy; five have been well since a third or fourth course of therapy, but the period of observation in these cases is brief. (Table XIV.) Numerous additional patients, experiencing mild recurrences shortly after treatment, have been managed satisfactorily by conservative measures without corticoids for relatively long periods.

Forty-four patients in remission are leading useful lives, taking small regular doses of ACTH intramuscularly or steroids orally (Table XV); in four such patients the symptoms are controlled only partially.

TABLE XI
RECURRENCES AFTER STEROID THERAPY

Months	After First Course	After Subsequent Courses	Total Recurrences
<3	32	18	50
3–12	32	16	48
12–24	19	7	26
24–36	4	0	4
36–48	3	0	3
48–60	2	0	2
Total recurrences	92	41	133

TABLE XII
RELAPSES DURING STEROID THERAPY

Months	After First Course	After Subsequent Courses	Total Relapses
< 3	7	6	13
3–12	11	11	22
12–24	3	2	5
24–36	2	0	2
Total relapses	23	19	42

TABLE XIII
COURSE OF RECURRENCES

Patient's Status	After First Course	After Subsequent Courses
Required ACTH or steroids	75	36
Subsided on medical therapy	24	6
Continued activity	9	7
Required surgery	5	10
Died	2	1
Total recurrences	115	60 (46 patients)

TABLE XIV
REMISSIONS AFTER STEROID THERAPY

Months	After First Course	After Subsequent Courses	Total Remissions
< 3	4	4	8
3–12	4	2	6
12–24	6	3	9
24–36	5	1	6
36–48	2	3	5
48–60	6	1	7
Total remissions	27	14	41

PRESENT STATUS

The current clinical status appears to be excellent in thirty-seven patients; seventy-six are much improved, leading useful lives, although not entirely well; included in this group are the forty-four patients receiving maintenance

therapy. Of the 180 patients, thirty-five are classified as therapeutic failures, although nineteen of them live useful lives. Definitive surgery was necessary in seventeen patients, with good to fair results in all except one, who died of electrolyte imbalance elsewhere two years postoperatively. Twelve patients including this one are dead; four are lost to follow-up. (Table XVI.)

TABLE XV
REMISSIONS TO DATE—STEROID THERAPY MAINTAINED

Months	During First Course	During Subsequent Courses	Total Remissions
< 3	2	7	9
3–12	11	15	26
12–24	0	4	4
24–36	4	0	4
36–48	1	0	1
Total remissions	18	26	44

TABLE XVI
PRESENT STATUS

Normal life	37
Partial recovery: course improved	76
Course unchanged following therapy	36*
Surgical treatment	16
Dead	12
Lost to follow up	4
Total patients	180

* Nineteen lead useful lives.

COMPLICATIONS

Manifestations of hypercorticism, characterized most often by rounding of the face and acne, less frequently by hypertrichosis, striae and buffalo obesity, were prominent in 137 patients and minimal in forty-three. (Table XVII.) These changes were troublesome only in a few of the younger female patients who refused to continue ACTH therapy because of the temporary disfigurement. Edema occurred in 125 patients; it was controlled usually by salt restriction, occasionally by mercurial diuretics. Hypertension, noted in forty-one patients, did not present a difficult problem. Corticotherapy was discontinued only rarely because of side effects; however, if these changes were pronounced before clinical improvement had occurred, a poor therapeutic result could be anticipated.

Alkalosis developed in ninety-five patients; the serum CO_2 in fifty-nine ranged from 30 to 35 mEq./L.; in twelve patients it exceeded forty mEq./L. Hypokalemia was observed in forty-three patients. In twenty-five patients the serum potassium ranged from 3.0 to 3.5 mEq./L.; in eighteen it was less than 3.0 mEq./L. The chemical aberrations were corrected by decreasing the dosage or by complete withdrawal of corticotherapy, intravenous infusion of potassium chloride or, less frequently, by oral administration of potassium salts.

TABLE XVII
SIDE EFFECTS

Cushing-like changes:	
Minimal	43
Moderate	83
Severe	54
Electrolyte disturbances:	
Alkalosis	95
Hypokalemia	43
Carbohydrate metabolic disturbances:	
Hyperglycemia	24
Glycosuria	26
Psychoses (temporary)	10
Allergy to ACTH	9
Peptic ulcer	1

Hyperglycemia was noted in twenty-four patients, glycosuria in twenty-six. In four known diabetic patients the insulin requirements rose substantially; in three non-diabetic patients insulin was necessary temporarily but not after the termination of therapy. Leukocytosis was observed in eighty patients at some time during treatment; in fourteen, the white count exceeded 20,000 cells per cu. mm.

Adverse emotional changes were noted frequently, including severe depression and manic behavior; ten patients actually became psychotic. Two individuals committed suicide during ACTH therapy; a suicidal attempt by a third patient was unsuccessful. The emotional disturbances usually were temporary, subsiding upon reduction of dose or termination of therapy. Severe infections complicated treatment in five cases: severe pneumonitis, two; septicemia, two; tuberculosis in one patient, responding rapidly to appropriate therapy. Four patients were considered to have delayed wound healing following surgery. All were

malnourished as a result of prolonged, severe illness and had been on prolonged steroid therapy. In nine patients hypersensitivity to ACTH developed, which was manifested principally by urticaria; other symptoms included generalized pruritus, erythema, severe headache and tinnitus. Skin reactions were positive to both the Wilson and Armour preparations in the five cases tested; allergy has not been encountered in the past three years. An active peptic ulcer was observed in only one patient, although at least nine of the series had a history of peptic ulcer and a deformed duodenal bulb at x-ray; in the single instance, the ulcer healed during antacid therapy while steroids were maintained and symptoms have not recurred during many months of continued steroid treatment.

TABLE XVIII
TYPES OF OPERATIONS

Type of Operation	Number
Total colectomy-ileostomy:	
1 stage	6
2 stage	6
Partial colectomy-end to end anastomosis	2
Partial colectomy-ileostomy	1
Partial colectomy-ileo-transverse colostomy	1
Ileo-transverse colostomy (side-tracking procedure)	1

TABLE XIX
INDICATIONS FOR OPERATION

Indication	Number
Fulminating course plus hemorrhage*	2
Fulminating course*	2
Severe prolonged activity*	3
Recurrent activity*	6
Recurrent iridocyclitis*	1
Progressive rheumatoid arthritis*	1
Mass right lower quadrant	1
Carcinoma colon	1

* Poor initial response or decreasing response to repeated courses of corticoid therapy.

ANALYSIS OF SURGERY

Seventeen patients required surgery, principally total colectomy and ileostomy. (Table XVIII.) The usual indication for operation was severe disease not responding to intensive medical treatment including steroids; in four cases the colitis had become fulminating. (Table XIX.) L. C., a seventeen year old girl, underwent a segmental resection of the transverse colon with a primary end-to-end anastomosis. She had experienced frequent recurrences while on maintenance hydrocortisone therapy; however, the extent of involvement, as determined radiologically, was confined to the transverse colon and had not changed over a period of several years; she remains well at the present time. M. K., a twenty year old boy, with a similar history of recurrences, had segmental colitis by x-ray. At operation, skip areas of involvement were discovered in the ileum as well as in the ascending and transverse colon; an ileo-transverse colostomy was established. A subsequent recurrence of symptoms required hospitalization and renewed corticoid therapy. The indications for operation in four cases were recurrent iridocyclitis, progressive rheumatoid arthritis, unexplained mass in the right lower abdominal quadrant later shown to be inflammatory, and carcinoma of the colon.

TABLE XX
ANALYSIS OF DEATHS
(12 PATIENTS)

Probably Related Directly to Ulcerative Colitis and/or Steroid Therapy—Six Patients	
1. Peritonitis	Onset antedated ACTH therapy
2. Sudden unexplained death	During ACTH therapy
3. Fulminating colitis, shock, renal failure	During ACTH therapy
4. Septicemia, pneumonia	During ACTH therapy
5. Suicide	During ACTH therapy
6. Suicide	During ACTH therapy
Indirectly Related to Ulcerative Colitis—Three Patients	
7. Electrolyte imbalance	38 months after ACTH therapy; 2 years after colectomy-ileostomy
8. Hemolytic anemia	During ACTH therapy
9. Fulminating hepatitis	During hydrocortisone therapy
Unrelated—Three Patients	
10. Rheumatic heart disease	
11. Cholangitis	
12. Pulmonary complications secondary to varicella	

ANALYSIS OF DEATHS

There were twelve deaths. (Table XX.) At least six of the fatalities appear unrelated to

steroids, or to active ulcerative colitis, although two patients were receiving maintenance corticotherapy at the time of death. H. B. died at another hospital, thirty-eight months after a temporarily helpful course of ACTH therapy and two years after an ileostomy had been performed elsewhere; the cause of death was thought to be an electrolyte imbalance. W. P. responded to a thirty-day course of ACTH but six months later died of severe hemolytic anemia. C. E. responded slightly to corticotropin during the first half of 1952; however, the colitis gradually subsided and remained quiescent to the time of his death in January, 1955, from congestive heart failure secondary to rheumatic heart disease. S. S. received small amounts of ACTH and cortisone from January, 1952, through May, 1953, with sustained improvement; however, one year later he died of a cholangitis. M. F. died of pulmonary complications secondary to varicella, twenty months after a nineteen-day course of corticotropin; the colitis was inactive at the time of death. E. T., while receiving hydrocortisone, died of acute necrosis of the liver complicating infectious hepatitis; at autopsy the colitis appeared to be entirely healed.

The remaining six deaths occurred during corticotherapy and in some way could be related directly to hypercorticism. B. G., one of the first patients treated with ACTH, died of generalized peritonitis secondary to a perforation of the cecum and abscess formation, antedating ACTH therapy; the spread of the infection may have been abetted by a high steroid level. E. K., during her third course of corticotherapy for severe recurrent colitis, responded poorly; surgery was contemplated but she suddenly died; an autopsy was not obtained. N. M., acutely and critically ill, seemed to respond to intravenous corticotherapy but sudden shock, coma, renal failure and jaundice resulted in death within several days; an autopsy was not obtained. In R. G., a debilitated elderly woman who had undergone operation previously for regional enteritis, recurrent ileocolitis reponded satisfactorily to ACTH. During the fourth week of therapy weakness, fever, shock and coma suddenly developed and the patient died despite all therapeutic efforts; pre- and postmortem blood cultures revealed pseudomonas aeruginosa. E. R. and T. Z. unexpectedly committed suicide on the twenty-seventh and twenty-ninth days of therapy, although the colitis in each case had improved.

COMMENT

The favorable clinical response to ACTH and related compounds in 164 of 180 patients emphasizes the beneficial effects of these substances. The results are noteworthy since they were achieved in a group of patients with severe or moderately severe disease who had been treated without sustained benefit; surgery had been recommended elsewhere frequently. The ineffectiveness of placebos and the lack of significant or continued improvement on conservative therapy alone would appear to minimize the role of suggestive or psychotherapeutic factors. Qualitatively, the clinical effect was similar to that characterizing effective medical therapy without steroids, but the response to corticoids was far more rapid, uniform and more dramatic than could have been anticipated with conventional treatment. Comparison of the present series with a group of 100 patients treated before the adrenal steroids were available indicates a higher incidence of favorable therapeutic results, a smaller number of patients requiring surgery and a lower mortality rate in the current series; although the two groups are not completely identical, the findings further emphasize the usefulness of the adrenal steroids as adjunct therapy.

Aqueous corticotropin was the most potent and consistently effective of the compounds studied. The intravenous route induced maximal adrenocortical stimulation; intramuscular administration appeared to be somewhat less effective but the practicality of intramuscular injection outweighed the slight loss of potency. Next in order of effectiveness were hydrocortisone intravenously and orally, corticotropin gel (which was not of uniform potency), prednisone and prednisolone, and cortisone. Theoretically, there should have been little difference between comparable doses of aqueous and long-acting corticotropin preparations; clinically, the gel did not seem to be as reliable. In patient H. K., acutely ill with moderately severe ulcerative colitis, corticotropin gel in divided doses up to 120 units daily failed to produce significant improvement or marked eosinopenia. Aqueous ACTH was instituted in the identical dose, with rapid, most dramatic improvement. The particular lot of gel in question had produced eosinopenic responses in other patients. The explanation for the failure of corticotropin gel to activate the adrenal cortex in this and other

patients is not apparent; other investigators have made similar observations [*5*].

Hydrocortisone orally, as reported previously [*6*], seems capable of producing significant clinical improvement with fewer side effects than are observed with ACTH in quantities required to produce a comparable clinical response. Hydrocortisone also has been administered in retention enemas, apparently with favorable results [*7*]. Prednisone and prednisolone have been prescribed less often but the results have been encouraging, suggesting that these newer agents, in high dosage (60 to 100 mg. daily), are capable of effectively controlling symptoms with fewer side effects. Cortisone, although a potent drug in high dosage (200 to 300 mg. daily), is associated with a high incidence of side effects; the sole advantage of cortisone is that it can be administered intramuscularly and thus utilized in the preoperative preparation of patients on long-term steroid therapy.

The decreasing clinical response during prolonged administration of ACTH or with successive courses of corticotropin has been noted also by other investigators [*8,9*]. This relative state of refractoriness, in our experience, has occurred with oral steroids as well. The cause of this troublesome phenomenon is not known. Increasing severity of the disease would explain the decreasing response to both ACTH and oral steroids. Circulating antihormones or antibodies against corticotropin may be a factor; inactivation of the material in the tissues at the site of injection, with delayed or decreased release of hormone into the blood stream is a third possibility. Intravenous administration of the drug occasionally has overcome the refractory state, supporting the last hypothesis and militating against the antihormone theory, although intravenous infusion may evoke a "load" of hormone in excess of the neutralizing ability of the "anti-substances." The relative clinical superiority of ACTH compared to other corticoids is not entirely understood. This impression may be related to the use of initial doses of corticotropin relatively higher than initial doses of the oral steroids. Hydrocortisone, for example, was prescribed in an amount somewhat less than twice that of ACTH; there is evidence suggesting that one unit of ACTH is equivalent to at least 2 mg. of hydrocortisone [*10*]. Another explanation may be that adrenal cortical stimulation releases a spectrum of hormones whose effects excel that of any single steroid administered from without; exogenous steroids are known to depress normal cortical function [*11–13*].

The frequency of side effects is not surprising in view of the large quantities of corticoids prescribed and the long duration of treatment. However, serious complications attributable to these agents were uncommon. The manifestations of the Cushing-like state were related to the inherent physiologic activity of the hormones. The high incidence of alkalosis and hypokalemia seems attributable to the infrequent administration of potassium salts routinely, because of the hazard of increasing the diarrhea. The profound mental changes with high circulating levels of steroids present a serious problem. Chlorpromazine has been helpful in controlling some of these. The development or reactivation of a peptic ulcer was encountered in only one patient, although nine in this series are known to have had a peptic ulcer by history or by x-ray. The absence or lack of activation of peptic ulcer during the prolonged administration of adrenal steroids in ulcerative colitis also has been recorded by other investigators. Streeten and Pollard [*14*] noted peptic ulcers in twenty-one of 730 patients receiving corticotropin or adrenal steroids for various diseases, an incidence of only 2.9 per cent. Giant ulceration of the colon did not occur in this series; such lesions existing prior to therapy were observed radiologically to heal during the administration of corticoids. The incidence of severe hemorrhage appeared to be no greater in the present series than in patients not receiving steroids; massive bleeding from the colon ceased dramatically on at least one occasion upon the administration of corticotropin intravenously. In the group reported by Maltby, severe hemorrhage, though it had occurred in seven patients before the use of ACTH, did not develop during steroid therapy. Perforation of the bowel was present in only one patient, antedating the ACTH therapy;* perforations had occurred in six of 100 patients treated prior to 1948 [*15*]. In a controlled study under the auspices of the British Medical Council [*3*], 101 patients with ulcerative colitis were treated without steroids and 109 with cortisone; two perforations occurred, both in the control group. Perforation of the colon did not occur in the 109 patients reported by Maltby [*4*]. The routine

* Recently, a patient, observed after the present series was completed, died of fulminating ulcerative colitis with perforation of the bowel and peritonitis. Therapy had included ACTH. The colon had been markedly distended.

use of sulfonamides, the frequent administration of penicillin and streptomycin and the constant therapeutic effects to restore and maintain adequate nutrition may have contributed significantly to the absence of perforations in the present series.

Although ACTH and related compounds effectively controlled the symptoms of ulcerative colitis in the majority of patients, the over-all recurrence rate of 70 per cent suggests that these agents *per se* do not necessarily cure the disease. However, the rate of recurrence was appreciably lower in the few patients receiving steroids in the early stages of their illness. Similar observations were reported in the British series. It is conceivable that steroids given early in the course of ulcerative colitis, when the anatomic changes are comparatively slight, can suppress the inflammatory process effectively and thus prevent extensive damage to the colon. Another important role for ACTH is the definitive treatment of fulminant colitis occurring as the first manifestation of the disease. Ultimate restoration of such patients to normal health without surgical measures has been accomplished. The serial biopsy studies by Truelove, Horler and Richards [*16*] and the observations of Levine, Kirsner and Klotz [*17*] indicate that the beneficial effects of steroids upon the symptoms of ulcerative colitis are accompanied with definite histologic evidences of healing. Truelove has suggested continuation of steroids until such evidence of healing is obtained.

Treatment with small doses of ACTH or oral steroids has been continued beyond one year in sixteen patients; nine have been symptom-free but seven have experienced recurrences. Because ulcerative colitis is an unpredictably remittent disease, indefinite maintenance therapy has not been considered practical. In those patients, however, in whom recurrent activity manifests itself as the dose is reduced and control again is achieved by a moderate but well tolerated increase in the quantity of steroids, prolonged maintenance therapy may be contemplated.

The mechanism of the remissions induced by the corticoids is unknown. Certain theoretic possibilities, including the possible relationship of ulcerative colitis to disorders of connective tissue and to hypersensitivity phenomena, have been discussed in previous papers [*1,2,6,18*]. Recent experimental work in our laboratory in which a form of ulcerative colitis was induced in the colon of rabbits sensitized to foreign protein [*19*] increases interest in the possible participation of hypersensitivity mechanisms in the pathogenesis of ulcerative colitis. Comparison of the actions of steroids and of salicylates, as reported for rheumatoid arthritis and rheumatic fever, is not pertinent in ulcerative colitis, since in this disease salicylates frequently aggravate rather than ameliorate the symptoms. Continued study of the effects of corticotropin and the adrenal steroids upon the disease in man and upon experimental colitis in animals is needed and may provide important clues to the understanding of this difficult but intriguing problem.

SUMMARY

Since January, 1950, 180 patients with ulcerative colitis have been treated with ACTH, cortisone, hydrocortisone and the newer analogues. In most instances these agents were prescribed as adjuncts to a comprehensive medical program. The disease was classified clinically as severe or moderately severe in 92 per cent of the patients. Steroid therapy was initiated with corticotropin in 134 patients, with hydrocortisone in twenty-nine cases and in the remaining seventeen with either cortisone, prednisone or prednisolone.

An immediate beneficial effect was observed in 85 per cent of the patients. The response to corticotropin was more dramatic and more uniform than to the other agents; the beneficial effects included subsidence of fever, tachycardia, abdominal distress, and blood in the feces, together with increase in appetite and a pronounced sense of well being. The bowel movements decreased in frequency and the discharges improved in consistency, although somewhat more slowly. Proctoscopic improvement occurred in the majority of patients but less rapidly than the clinical response.

Symptoms recurred in 70 per cent of the patients. The recurrence rate in those with a relatively brief history was lower than the overall figure. Repeated courses of corticotherapy induced favorable responses in the majority of ninety-one patients. However, the results were not as striking as in the first course. At present, 113 patients are considered to be in complete or partial remission; forty-four continue on steroid therapy. Thirty-nine patients have been in remission since the first course; the remainder have received multiple courses. Thirty-five

patients are unimproved. Seventeen patients have undergone surgery, twelve have died (including one of the surgical group), and four have been lost to follow-up.

The most common side effects were Cushing-like changes in 137 patients, alkalosis in ninety-five, hypokalemia in forty-five and hyperglycemia or glycosuria in twenty-six; these untoward effects seldom were severe enough to discontinue therapy. The more serious but less frequent complications included temporary psychosis in ten, two suicides, allergy to ACTH in nine, and severe infections in five. Peptic ulcer developed in only one patient; nine individuals with peptic ulcer received large doses of steroids without untoward effects.

ACTH produced more frequent and the most profound side effects but, in general, was the most effective compound. Hydrocortisone, prednisone and prednisolone were less effective but often produced comparable clinical results with fewer side effects. Cortisone did not compare favorably with the other corticoids.

CONCLUSIONS

1. ACTH and related compounds, although potentially hazardous, are comparatively safe adjuncts to the conventional treatment of ulcerative colitis when administered in sufficient quantities and with adequate precautions.

2. These potent compounds usually ameliorate the course of the disease and often are dramatic in their clinical effects. Anatomic evidence of healing occurs, but more slowly.

3. The mechanism of action of corticotropin and the adrenal steroids in ulcerative colitis is not clear; their ultimate role in the treatment of ulcerative colitis is yet to be determined.

REFERENCES

1. Kirsner, J. B. and Palmer, W. L. Ulcerative colitis: therapeutic effects of corticotropin (ACTH) and cortisone in 120 patients. *Ann. Int. Med.*, 41: 232, 1954.
2. Kirsner, J. B. and Palmer, W. L. Effect of corticotropin (ACTH) in chronic ulcerative colitis: observations in forty cases. *J. A. M. A.*, 147: 541, 1951.
3. Truelove, S. C. and Witts, C. J. Cortisone in ulcerative colitis. *Brit. M. J.*, 2: 4947, 1955.
4. Maltby, E. J., Dickson, R. C. and O'Sullivan, P. M. The use of ACTH and cortisone in idiopathic ulcerative colitis. *Canad. M. A. J.*, 74: 4, 1956.
5. Streeten, D. H. P. and Seltzer, H. S. Instances of failure of high potency ACTH gel to activate the adrenal cortex. Unpublished data presented before Michigan Chapter, A. C. of P. at Detroit, Michigan, 1955.
6. Kirsner, J. B., Sklar, M. and Palmer, W. L. The use of hydrocortisone in ulcerative colitis: preliminary observations. *Ann. New York Acad. Sc.* 61: 384, 1955.
7. Allodi, A. and Muratori, F. Fifth International Congress of Gastroenterology. London, 1956.
8. Elliot, J. M. and Giansiracusa, J. E. ACTH and cortisone in the treatment of ulcerative colitis. An evaluation of their prolonged administration. *New England J. M.*, 25: 969, 1954.
9. Wirts, C. W., Rehfuss, M. E. and Yantes, H. A. Long-term results in corticotropin-treated ulcerative colitis. *J. A. M. A.*, 154: 36, 1954.
10. West, H. F. Purified ACTH gel—control of therapy in rheumatoid arthritis. *Ann. Rheumat. Dis.*, 13: 56, 1954.
11. Engleman, E. P., Krupp, M. S., Johnson, H. P., Welsh, J. E., Wrenn, H. T. and King, W. R. Adrenocortical function during continuous long-term therapy with cortisone. *Arch. Int. Med.*, 91: 1, 1953.
12. Sprague, R. G. Cortisone and ACTH: a review of certain physiologic effects and their clinical implications. *Am. J. Med.*, 10: 567, 1951.
13. Fredell, E. W., Johnson, H. P., Krupp, M. A., Engleman, E. P. and McGrath, A. K. Adrenocortical function during long-term cortisone therapy. *Arch. Int. Med.*, 95: 411, 1955.
14. Streeten, D. H. and Pollard, H. M. Reported at Pan American Congress of Gastroenterology, Havana, Cuba, 1956.
15. Kirsner, J. B., Palmer, W. L., Maimon, S. N. and Ricketts, W. E. Clinical course of chronic nonspecific ulcerative colitis. *J. A. M. A.*, 137: 922, 1948.
16. Truelove, S. C., Horler, A. R. and Richards, W. C. D. Serial biopsy in ulcerative colitis. *Brit. M. J.*, 2: 1590, 1955.
17. Levine, M. D., Kirsner, J. B. and Klotz, A. P. A new concept of the pathogenesis of ulcerative colitis. *Science*, 114: 522, 1951.
18. Kirsner, J. B. and Palmer, W. L. Ulcerative colitis: considerations of its etiology and treatment. *J. A. M. A.*, 158: 341, 1954.
19. Elchlepp, J. G. and Kirsner, J. B. Studies on experimental ulcerative colitis. *Proc. Cen. Soc. Clin. Res.*, 28: 27, 1955.

Seminar on Bone Disease

Calcium and Phosphorus Metabolism*

D. Harold Copp, M.D.
Vancouver, Canada

Calcium and phosphorus are the principal mineral constituents of the skeleton, which contains over 99 per cent and 90 per cent of the total body content of each respectively. For this reason, it is not surprising that bone is intimately involved in the metabolism of both elements, and that bone disease is frequently associated with disturbances in calcium and phosphorus. In addition, both elements have very important functions in the cellular "soft tissues."

The present review will be confined to some of the more important aspects of calcium and phosphorus metabolism, and because of limitation of space, no attempt will be made to give a detailed and exhaustive treatment. Fortunately, a number of excellent reviews, conference reports and books have been published in recent years dealing with this field [*1–14*].

CALCIUM METABOLISM

The body contains approximately 1½ per cent calcium by weight, and almost all of this is located in the skeleton. Mitchell analyzed the body of a normal 70 kg. adult man and found 1,114 gm. in the skeleton, 11 gm. in the soft tissues (chiefly intracellular) and less than 1 gm. in blood and extracellular fluid [*15*]. However, this small amount of calcium plays a vital role in the function of the body, affecting enzyme activity, membrane permeability and neuromuscular excitability. The homeostasis of calcium in blood and extracellular fluid would appear to be of great biologic importance, for it is one of the best-regulated levels in the body. A fall in serum calcium level may produce tetany and death, while hypercalcemia produces functional disturbances and cardiac effects.

Ca^{45} Studies. The availability of radiocalcium (Ca^{45}) and radiophosphorus (P^{32}) has made possible measurements of the movement of these elements between blood, body fluids and tissues, and studies of the kinetics of uptake and exchange with the calcium and phosphorus present in the skeleton. When radiocalcium is injected intravenously, it disappears rapidly from the blood, moving into interstitial space and bone. The kinetics of the blood disappearance curve have been analyzed for rats, rabbits, cattle and humans [*16–19*]. Armstrong found that approximately half the blood calcium in the rat exchanged with calcium in the interstitial fluid per minute, so that the two may be considered as essentially a single compartment [*16*]. There is also very rapid movement of Ca^{45} into bone, the limiting factor apparently being the bone blood flow. Frederickson, Honour and Copp [*20*] determined the initial bone clearance of Ca^{45} from blood in the rat and obtained a value of 5 to 8 per cent of the cardiac output. Similar values have been obtained with Sr^{90} and P^{32} [*21*]. If the initial clearance of these isotopes by bone is complete, this will be a measure of bone blood flow, which in any case can be no less than this value.

Bauer, Carlsson and Lindquist [*22–24*] have studied the kinetics of turnover of Ca^{45} and P^{32} in bone in rats and children. By an ingenious series of calculations, they have been able to estimate the exchangeable calcium in bone, calcium uptake or accretion, and calcium resorption. In a young rat, they estimated for tibia an accretion rate of 6.2 per cent of the bone Ca/day; a resorption rate of 4.7 per cent of the bone Ca/day; and an exchangeable fraction equivalent to 3.0 per cent of the total calcium in the bone [*22*].

In children, the accretion rate was 1.6 per cent of the bone phosphorus in twenty-four hours

* From the Dept. of Physiology, University of British Columbia, Vancouver. Supported in part by grants from the Division of Medical Research, and the Associate Committee on Dental Research of the National Research Council, Canada.

(six month infant), 0.83 per cent in untreated rickets (seven month infant) and 1.25 per cent in the same infant after adequate treatment with vitamin D [*24*]. The increased new bone formation in the children treated with vitamin D was accompanied by a corresponding increase in the resorption rates.

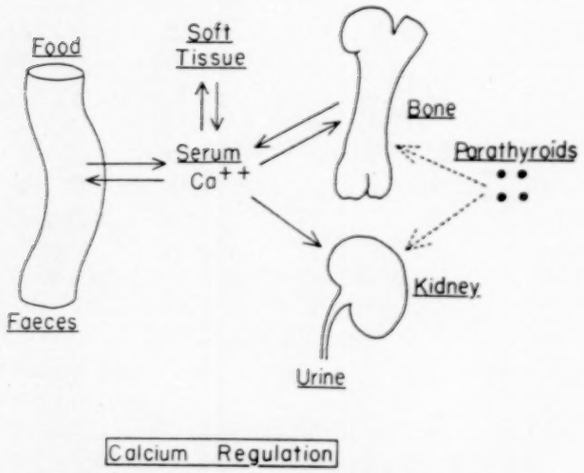


FIG. 1. Factors involved in serum calcium regulation.

Long term studies of bone retention of Ca^{45} indicate that the turnover of the total bone calcium is very slow [*25,26*].

Calcium Balance. The serum calcium level depends on a balance between calcium added from intestinal absorption and bone resorption, and calcium lost from blood by excretion in urine and feces and deposition in bone salt. In the young animal, the latter occurs primarily in areas of bone growth and remodelling, but even in the adult there is some deposition of new bone in forming osteons [*27*]. The factors involved in this calcium balance are illustrated in Figure 1.

Intestinal Absorption. Sherman recommends a daily dietary intake of 0.65 gm. calcium per day by adults; 1.00 gm. by children and still higher intakes in pregnancy and lactation when the needs for calcium are increased [*28*]. Howard [*29*] has pointed out that a normal individual in calcium balance excretes only 100 to 150 mg. Ca per day in urine, so that this must represent *net* absorption from the gut. However, such an individual may actually be absorbing 600 to 800 mg. of the dietary calcium, and excreting 500 to 700 mg. in the intestinal tract. Assuming that 8 liters of digestive juices are formed per day, this alone would contain approximately 500 mg. Ca. Bronner and Harris [*30*] studied absorption of Ca^{45} in boys aged eleven to sixteen and in two young adults. Determining fecal Ca^{45} and estimating absorption by difference, they obtained values from 30 to 80 per cent; fecal excretion of intravenously injected Ca^{45} was 3 to 5 per cent.

Net absorption from the gut appears to be determined more by need than intake. Howard, Parson and Bigham [*31*] increased the daily dietary intake of a number of bedridden patients from 0.2 gm. to 2.2 gm. with no appreciable increase in calciuria. However, absorption of dietary calcium may be modified by a number of other factors. It is apparently favoured by Vitamin D [*6*], high protein diet [*32*] and a state of calcium depletion [*33*]. Vitamin D deficiency [*6*], and increased phosphate [*34*] or phytic acid [*35,36*] in the diet reduces calcium absorption.

While net intake is regulated by the intestine, elimination appears to be regulated primarily by the kidneys, for when active bone resorption is taking place, the excess calcium is excreted in urine rather than in feces [*31*]. In assessing the kidney function in calcium regulation, it must be remembered that 9 to 12 gm. of calcium are filtered by the glomerulus every twenty-four hours, and over 99 per cent of this is reabsorbed by the tubules [*37*]. Even in cases of hypercalcemia, only a small part of the filtered calcium appears in the urine. It is obvious that even small changes in the tubular reabsorption of calcium will result in very significant increases in urinary excretion. This may occur in immobilization of the patient and thyrotoxicosis [*31,38*]. In these cases, the increased urinary excretion occurs without any significant rise in the serum calcium level. In severe phosphorus deficiency in rats, with progressive osteoporosis, the calcium clearance may increase ten to twenty times, with normal or slightly sub-normal serum calcium levels [*39*].

Homeostatic Regulation of Serum Calcium. The normal serum calcium level is approximately 10 mg. per cent with a range from 9 to 11 mg. per cent. Depending on the method used, 50 to 70 per cent of the serum calcium appears to be ultra-filtrable and diffusible; the remainder is bound to protein [*40,41*]. There is remarkable precision in its homeostatic regulation, despite the large and variable movements of calcium in and out of the blood pool. In this process, the reservoir of calcium in bone is primarily in-

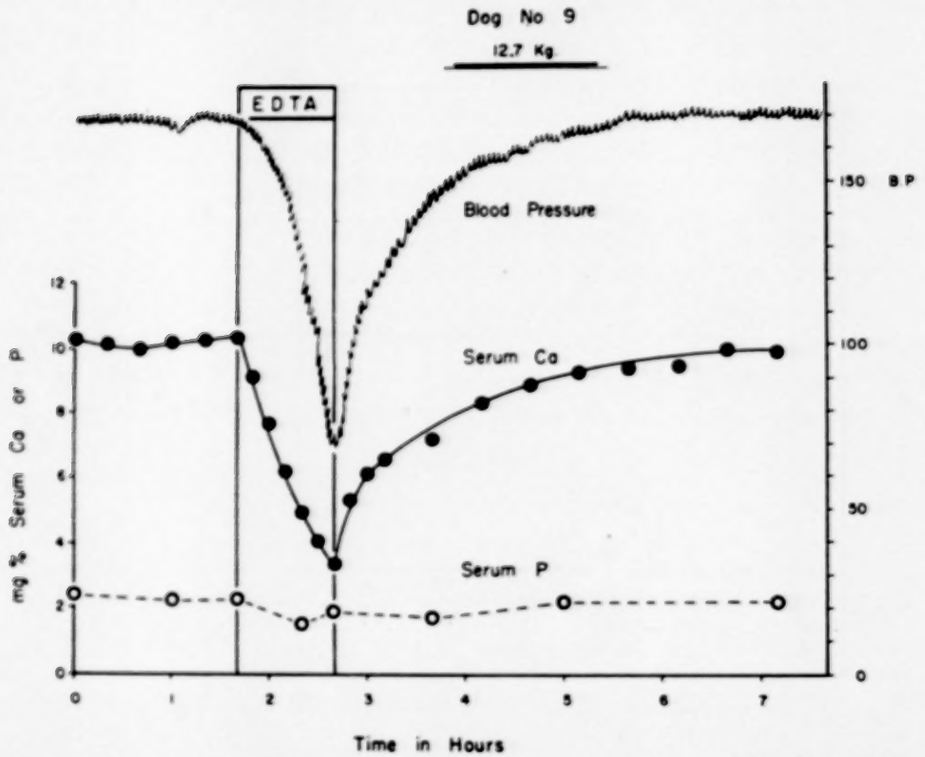


FIG. 2. Calcium mobilization from bone. Changes in serum calcium and phosphorus during infusion of Na_2-EDTA (sufficient to chelate and remove 10 mg. Ca/kg./hr.) and recovery period.

volved, although the parathyroid glands are also important. Following parathyroidectomy the serum calcium level falls in a few hours to 5 to 7 mg. per cent, while hyperparathyroidism produces hypercalcemia [*42*].

The amazing capacity of the skeleton to restore and maintain a normal serum calcium level has been demonstrated in a number of experiments in which hypocalcemia was produced by a variety of experimental procedures. Hastings and Huggins [*43*] carried out replacement transfusions in dogs, using blood from which most of the calcium and phosphorus had been removed by shaking with lead phosphate. Even when 50 per cent of the blood volume was replaced with hypocalcemic blood every ten minutes, it was extremely difficult to lower the blood calcium to a level which would produce tetany, and as soon as the procedure was stopped, the level promptly rose. They estimated that during the course of one experiment, the amount of calcium mobilized from bone corresponded to more than four times the amount present in the blood and interstitial fluid.

In other experiments, the serum calcium level was lowered by injections of oxalate, citrate or disodium EDTA [*44–46*]. In each case, the serum calcium rapidly returned to normal by mobilization from bone, once the procedure for producing hypocalcemia was stopped.

In this laboratory, quantitative measurements have been made of the mobilization of calcium from the skeleton in fasted dogs, in which hypocalcemia was produced by intravenous infusion of disodium ethylenediaminetetraacetate (Na_2-EDTA) [*47*]. This substance forms a relatively non-toxic chelate complex with calcium which has such a low dissociation constant that the calcium is to all intents removed from the biologic system. When an equivalent amount of the calcium EDTA was infused, no changes were observed in blood pressure, non-EDTA serum calcium level or general condition of the animal. The Na_2-EDTA was infused intravenously and at a continuous rate for one hour; the amount given was such as to chelate 10 mg. Ca per kg. body weight during this period. Serum calcium values were determined by photometric titration with Na_2-EDTA, using a modification of the method of Lehmann [*48*]. A typical curve show-

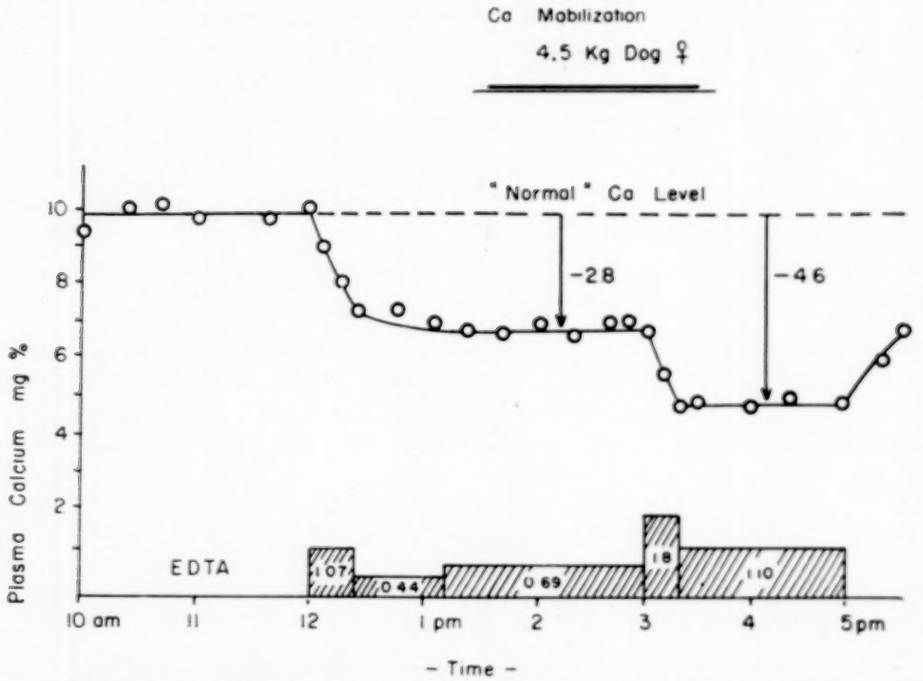


FIG. 3. Calcium mobilization from bone. Serum calcium levels during infusion of Na_2-EDTA at a rate adjusted so that calcium removal by EDTA is just balanced by calcium mobilization from bone.

ing serum calcium and phosphorus values during the control period, EDTA infusion and recovery is shown in Figure 2.

By analyzing these curves, mobilization of calcium from bone may be determined and related to the degree of hypocalcemia during the mobilization period. In studies on some thirty dogs, it was found that the rate of calcium mobilization was directly proportionate to the lowering of the serum calcium level. This suggests that an equilibrium exists between serum and a mobilizable calcium fraction in bone; the equilibrium is such that the serum calcium in the hypocalcemic blood flowing through the bone blood vessels is restored to normal by addition of calcium from this pool. Assuming that this is the case, the effective bone blood flow necessary to account for this mobilization may be estimated, and was found in our animals to range from 3 to 7 per cent of the resting cardiac output. This relationship between calcium mobilization and hypocalcemia was confirmed in dogs in which the rate of Na_2-EDTA infusion was adjusted so that a constant depressed level of serum calcium was maintained by balancing EDTA removal against calcium mobilization. A representative curve is shown in Figure 3.

Effect of Parathyroids. The parathyroid glands have an extremely important function in calcium metabolism, yet despite a voluminous literature and a number of excellent reviews, there is still no clear picture of the exact mode of action of the hormone [*48–52*]. Albright and Ellsworth [*53*] in 1929 proposed what is now termed the renal or phosphaturic theory of parathyroid action, based on their observations on a patient with hypoparathyroidism treated with parathyroid extract. They observed a marked increase in phosphate excretion in urine following administration of parathyroid extract, accompanied by a rise in the serum calcium level. They suggested that the primary effect of the hormone was to increase phosphate excretion, resulting in a lowering of serum phosphate, withdrawal of phosphorus from bone and mobilization of calcium—thus producing hypercalcemia. However, Thomson and Pugsley [*54*] in 1932 and Collip et al. [*55*] in 1934 observed a direct action of parathyroid extract on bone in nephrectomized animals, and concluded that the primary effect was stimulation of osteoclastic activity in bone. At present, the great weight of evidence appears to support the view that the primary effect of the parathyroid hormone in calcium regulation is on bone, since the characteristic effects—hypercalcemia and bone resorp-

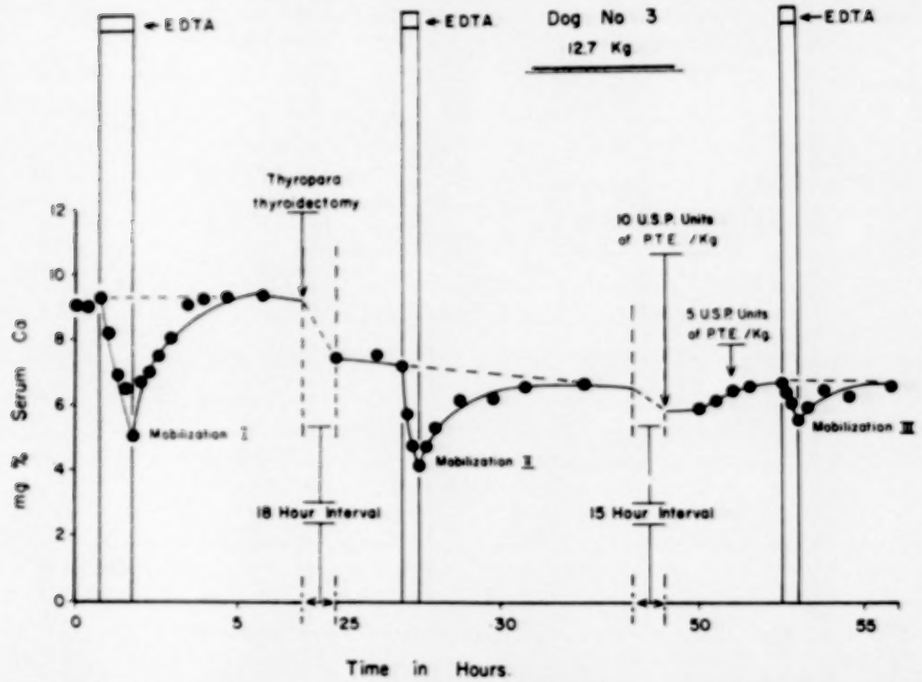


FIG. 4. Effect of parathyroidectomy on calcium mobilization. Changes in serum calcium level during EDTA infusion and recovery, before and twenty hours after thyroparathyroidectomy.

tion—may be produced in the nephrectomized animal [*56,57*]. Barnicot [*58*] and Chang [*59*] have also demonstrated a localized resorption of bone when parathyroid grafts were placed in close proximity to it.

Talmage and Elliott [*60*] nephrectomized rats and washed the peritoneal cavity three times daily with 30 ml. of an isotonic saline solution containing 3 per cent glucose and no calcium or phosphorus. The solution was left in the peritoneal cavity for one hour each time to permit equilibration with body fluids, and was then analyzed for Ca and P. In the control animals, the wash contained 7 mg. per cent Ca; after parathyroidectomy the value fell to 3.5 mg. per cent, along with a fall in phosphorus and citric acid. Administration of 1 I.U. parathyroid extract per hour for six hours restored all three values to normal.

In the parathyroidectomized dog the serum calcium fell to 6 to 7 mg. per cent within twenty-four hours [*61*]. In such parathyroidectomized animals, when Na_2-EDTA was infused, the serum calcium was reduced still further, but mobilization from bone restored the level to the new equilibrium value of 7 mg. per cent, and the "effective bone blood flow" measured at this level was found to be the same as that measured for a mobilization in the control period before the glands were removed [*61*]. (Fig. 4.)

McLean and Urist [*13*], in their excellent monograph on bone, have proposed a dual mechanism to explain the regulation of serum calcium. The first part of this mechanism, which operates in both normal and parathyroidectomized animal, is a diffusion equilibrium between serum and the labile fraction of the bone mineral and can maintain the serum calcium level at approximately 7 mg. per cent. The second part of the mechanism is dependent on the parathyroid glands and operates on the principle of a "feed-back." A fall in serum calcium level stimulates increased output of parathyroid hormone which in turn increases mobilization of calcium from bones causing a rise in serum level. It is this mechanism which they believe is responsible for maintenance of the normal level of 10 mg per cent.

Copp and Moghadam [*62*] carried out EDTA infusions in a dog immediately after thyroparathyroidectomy (Figure 5) and found that mobilization from bone was apparently normal, although the equilibrium gradually fell after the operation. While no direct "feedback" was possible in these animals, there was undoubtedly

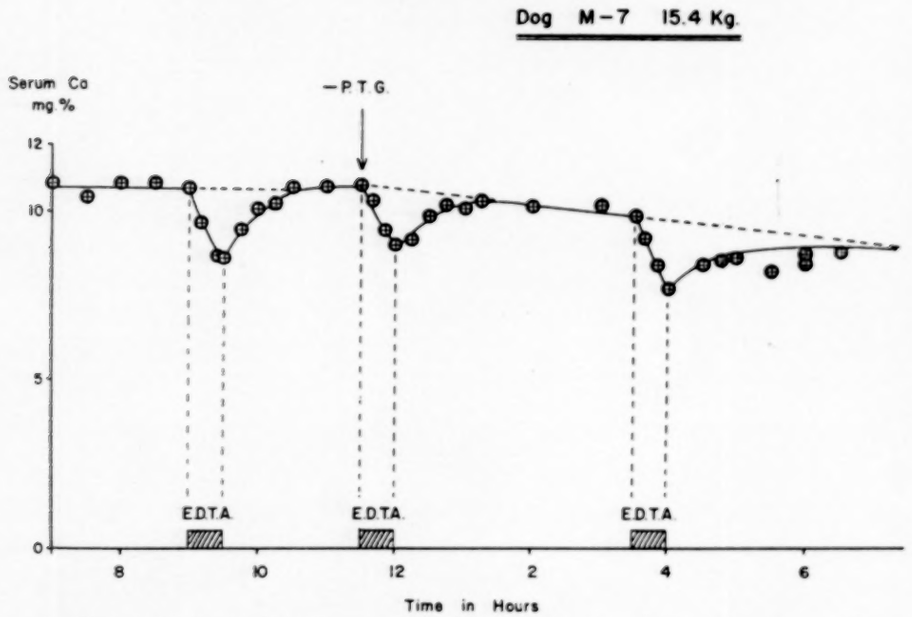


FIG. 5. Effect of parathyroidectomy on calcium mobilization. Changes in serum calcium level during EDTA infusion and calcium mobilization, before and immediately following thyroparathyroidectomy (indicated by: —P.T.G.).

parathyroid hormone present in the circulating blood. When parathyroid extract (E. Lilly preparation) was infused intravenously into parathyroidectomized animals at a constant rate, the serum calcium level rose gradually to normal and above normal [*62*]. (Fig. 6.) The calcium mobilization which accompanied EDTA infusion under these conditions was normal with respect to the new equilibrium level for serum calcium.

These results may best be explained on the basis of an equilibrium between serum calcium and a mobilizable calcium pool in bone. This pool must be accessible to the blood and may be related to the exchangeable calcium fraction. In the parathyroidectomized animals, this would correspond to a serum level of 5 to 7 mg. per cent; in the presence of functioning parathyroid glands or parathyroid hormone, this equilibrium value is raised to normal or even above normal. It would appear probable, as McLean suggests, that a feedback mechanism regulates the output of parathyroid hormone, which in turn affects the mechanism which determines the equilibrium between mobilizable bone calcium and blood.

Other Hormones. In birds, during one phase of the egg-laying cycle, or following administration of estrogens, there is extensive secondary development of spongy bone in the marrow cavities [*63*]. While the egg shell is calcifying, the serum calcium may rise to several times its normal value, but this is due to an increase in a physiologically inactive fraction, and the serum calcium ion concentration remains normal. Estrogens produce similar changes in mice and, within limits, the yield of new bone is proportionate to the dose given [*64*]. Marrow cavity may be entirely filled with this secondary spongy bone. In rats, estrogens have no effect in the adult, but apparently inhibit the normal resorption of the spongy bone beneath the growing epiphysis in young rats, so that the final result is an increase in the quantity of spongy bone present [*65*]. Estrogens have been administered to humans with osteoporosis, particularly of the senile or postmenopausal type, but with equivocal results [*66,67*].

Hypophysectomy in the immature rat leads to cessation of growth in bone associated with reduced activity in the epiphyseal cartilage of long bones [*68*]. Administration of growth hormone to such rats results in resumption of epiphyseal activity and growth in length of the bones. If growth hormone injections are continued for long periods of time in both hypophysectomized and normal rats, continued growth of the skeleton will give rise to giantism [*69*].

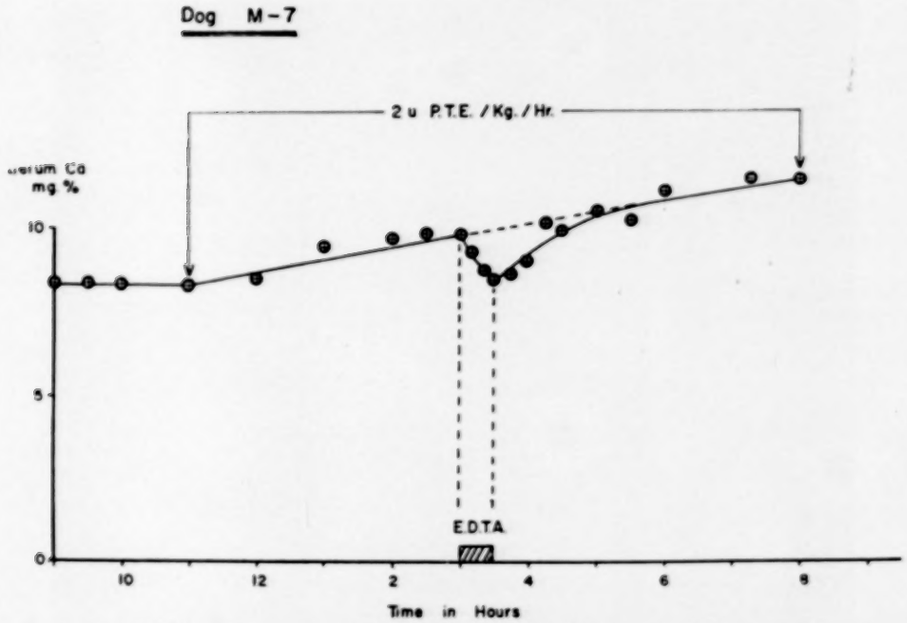


FIG. 6. Effect of parathyroid extract on calcium mobilization. Serum calcium in a dog thyroparathyroidectomized forty-eight hours previously and given continuous intravenous infusion of 2 I.U. para-thor-mone (E. Lilly)/kg./hr. for nine hours —Na_2EDTA infusion and measurement of calcium mobilization from bone carried out after four hours.

Thyroxin appears to have a synergistic action with growth hormone [*70*]. Large doses of thyroxin tend to accelerate the maturation of bone, while thyroidectomy retards development.

ACTH and cortisone both tend to suppress new bone formation, but do not interfere with normal resorption. This may account for the osteoporosis observed in Cushing's syndrome [*49*].

Vitamin D. Vitamin D favours the absorption of calcium and phosphorus from the intestinal tract and helps prevent the disturbances in serum calcium and phosphorus which lead to vitamin D deficiency rickets [*6*]. Bauer, Carlsson and Lindquist [*22*] have provided evidence that vitamin D increases the rate of bone resorption, thus freeing mineral for calcification of newly forming bone. Massive doses of vitamin D (over 50,000 I.U. per day) increase the mobilization of calcium and phosphorus from the skeleton, and have an effect not unlike that of parathyroid extract [*71,72*].

PHOSPHORUS METABOLISM

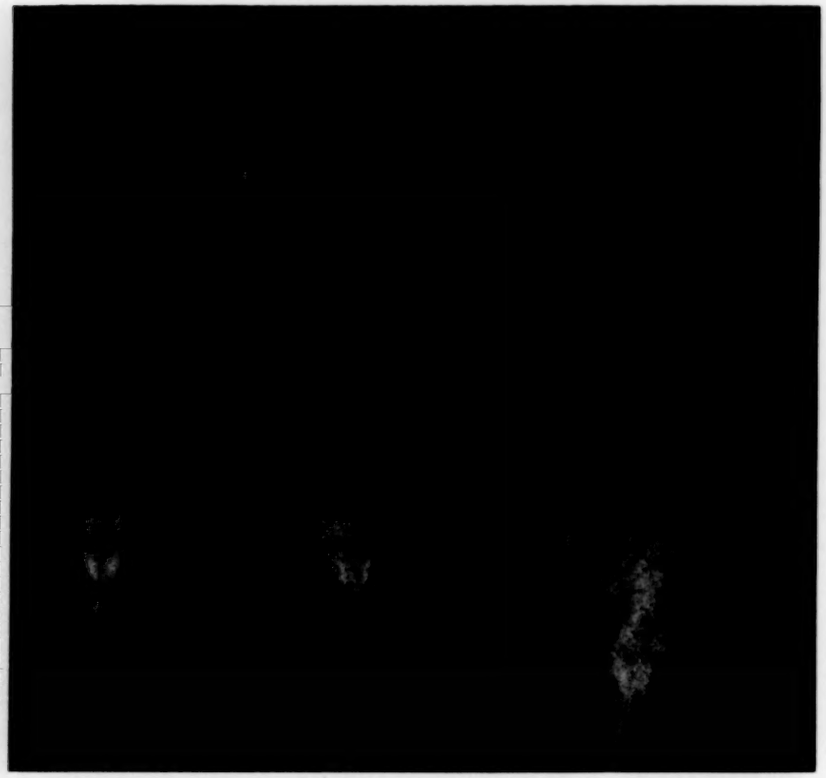
Approximately 90 per cent of the body phosphorus is found in the skeleton [*15*]. The remaining 10 per cent is chiefly intracellular, and plays an important role in the energy transfer mechanisms associated with cell metabolism.

The human diet is usually quite adequate in phosphorus. Sherman has estimated the minimum phosphorus requirements for the human adult at 0.88 gm. per day and has recommended an intake of 1.25 gm. per day [*28*]. The requirement is higher for growing children and women during periods of pregnancy and lactation.

On a normal diet, approximately two-thirds of the ingested phosphorus appears in the urine, so that a large proportion of the phosphorus in food must be absorbed. This has been confirmed in experiments using radiophosphorus [*73–74*]. Vitamin D favours phosphorus absorption [*6*]. Lack of vitamin D and presence in the intestinal tract of metallic ions such as iron, calcium and aluminum, which form insoluble phosphates, will reduce absorption [*75–77*].

There does not appear to be a very effective mechanism for regulating absorption of phosphorus from the intestinal tract, so that phosphorus balance is controlled primarily by variations in renal excretion. For this reason, in renal failure phosphorus continues to be absorbed and retained, leading to hyperphosphatemia.

Harrison and Harrison [*78*] observed an increase in the tubular reabsorption of phosphorus when rachitic puppies were given vitamin D, and consider this one of the important actions of the vitamin in raising the serum phosphate



7A 7B 7C

FIG. 7. Effect of severe phosphorus deficiency. Roentgenographs of (A) three week old rat at onset of experiment; (B) eight week old phosphorus deficient rat; and (C) eight week old control rat. Note severe osteoporosis in the deficient animal.

level and promoting calcification [*78*]. In phosphorus deficiency, there is also an increased renal reabsorption of phosphates, so that this ion disappears almost completely from the urine [*79*].

The parathyroid glands also have an important effect on phosphorus homeostasis and renal excretion [*80*]. This is decreased following parathyroidectomy, and increased when parathyroid extracts are administered [*81,82*]. Indeed, this phosphaturic effect of parathyroid extract is the basis for an assay test, using radiophosphorus (P^{32}) [*83*].

Serum Phosphate. In infants and young children, the serum inorganic phosphorus is 5 to 6 mg. per cent; this value diminishes with age until the adult value of 3 to 4 mg. per cent is reached. Reifenstein, Kinsell and Albright [*84*] suggest this difference in phosphorus level is due to the presence of growth hormone in children. Practically all the inorganic serum phosphorus is diffusible [*85*]. While changes in the serum level are characteristic of rickets and certain other disorders, hypophosphatemia does not produce dramatic effects such as the tetany associated with severe hypocalcemia.

Phosphorus Homeostasis and Severe Phosphorus Deficiency. While the kidneys appear to be far more important in phosphorus homeostasis than is the case for calcium, the reservoir of phosphorus in the skeleton is also of the greatest importance in maintaining adequate levels of this element in the tissues of the body. This is particularly well illustrated in the case of severe phosphorus deficiency [*86*]. Day and McCollum [*87*] first produced this deficiency in growing rats by restricting them to a diet containing only 0.017 per cent phosphorus. On this diet, growing rats went into negative calcium and phosphorus balance, and progressive osteoporosis developed, which eventually became so severe that the softened rib cage collapsed, and death from respiratory failure resulted [*87*]. Coleman et al. [*88*] have described histologic changes produced in the skeleton of animals restricted to such a phosphorus deficient diet. They found these changes resembled severe osteoporosis, combined with severe rickets. Some of the metabolic

changes have been described by Copp et al [*89*]. There is little or no change in the serum calcium level, but there is a marked fall in the serum phosphorus which may eventually reach a value of less than 1 mg. per cent. The phorphorus in the liver, muscle and other soft tissues remains normal, despite the negative phosphorus balance [*90*]. This is made possible by withdrawal of phosphorus from the bones and is accompanied by a marked calciuria and negative calcium balance. The eventual result is a very severe osteoporosis, which is most marked in the ribs and vertebrae. This may be seen in the roentgenograph shown in Figure 7 [*90*]. Oddly enough, the teeth remain relatively unaffected by the progressive osteoporosis, the molars are well mineralized and the incisors continue to grow and calcify. It is evident that in this severe phosphorus stress, the essential requirements of the living tissues of the body are met at the expense of the stores of phosphorus in the bones, even though this results in loss of rigidity and ability to provide support.

SUMMARY

The skeleton, which contains over 99 per cent of the body calcium and 90 per cent of the phosphorus, provides a reserve for the maintenance and regulation of these elements. Both have important functions in cells and body fluids.

Calcium balance depends on intake from the diet, loss in urine and feces and a balance between bone formation and bone resorption. Intake is regulated by intestinal absorption; excretion of excess calcium liberated by bone resorption occurs chiefly in urine.

The very precise homeostatic control of the serum calcium level depends on bone, parathyroids and kidneys. Mobilization of calcium from bone during hypocalcemia was found to depend on the extent to which the serum calcium was lowered, and on the bone blood flow. The latter has been estimated at 3 to 7 per cent of the resting cardiac output in the dog. There appears to be an equilibrium between a mobilizable calcium pool in bone and the serum calcium. This equilibrium level is 5 to 7 mg. per cent in the parathyroidectomized animal and 10 to 11 mg. per cent in the normal animal. It is probable that a "feedback" mechanism regulates the output of parathyroid hormone; the hormone in turn determines the equilibrium level between mobilizable bone calcium and blood.

A large part of the dietary phosphorus is absorbed and subsequently excreted by the kidney. The latter appears to be the main organ for regulation of phosphorus balance. In severe phosphorus deficiency, the requirements of the cellular soft tissues are met at the expense of the skeleton and severe osteoporosis develops. The bones, and particularly the ribs and vertebrae, become very thin and low in mineral, while the teeth are relatively unaffected.

Acknowledgments. Parathyroid extract (Parathor-mone®) was supplied through the courtesy of Eli Lilly and Company, Indianapolis.

The author is indebted to C. F. Cramer, J. M. Frederickson, K. Henze, E. Mensen, H. Moghadam and W. D. S. Thomas for assistance with some of the experimental work reported, and to E. C. Black and A. P. Suiker for assistance with the manuscript.

REFERENCES

1. Armstrong, W. D. Phosphorus metabolism in the skeleton. *Phosphorus Metabolism*, 2: 698, 1952.
2. Bergstrom, W. H. The skeleton as an electrolyte reservoir. *Metabolism*, 5: 433, 1956.
3. Howard, J. E. The metabolism of calcium and phosphorus in bone. *Bull. New York Acad. Med.*, 27: 24, 1951.
4. Howard, J. E. and Connor, T. B. A discussion of calcium homeostasis: the role of the skeleton and some speculations on the part played by the parathyroid hormone. *Bibliot. Paediat.*, (Suppl.), 58: 230, 1954.
5. Neuman, W. F. and Neuman, M. W. The nature of the mineral phase of bone. *Chem. Rev.*, 53: 1, 1953.
6. Nicolaysen, R., Eeg-Larsen, N. and Malm, O. J. Physiology of calcium metabolism. *Physiol. Rev.*, 33: 424, 1953.
7. Owen, E. C. Bone as a mineral reserve. *Brit. J. Nutrition*, 6: 415, 1952.
8. Transactions of the Macy Conference on Metabolic Interrelations, vol. 1–5, 1949–1953.
9. Ciba Foundation Symposium on Bone Structure and Metabolism. London, 1956. J. & A. Churchill Co.
10. Recent advances in the study of the structure, composition and growth of mineralized tissues. *Ann. New York Acad. Sc.*, 60: 541, 1955.
11. Calcium and phosphorus metabolism in man and animals with special reference to pregnancy and lactation. *Ann. New York Acad. Sc.*, 64: 279, 1956.
12. Bourne, G. H. The Biochemistry and Physiology of Bone. New York, 1956. Academic Press.
13. McLean, F. C. and Urist, M. R. Bone: An Introduction to the Physiology of Skeletal Tissue. Chicago, 1955. University of Chicago Press.
14. Stein, I., Stein, R. O. and Beller, M. L. Living Bone in Health and Disease. Philadelphia, Montreal, 1955. J. B. Lippincott Co.
15. Mitchell, H. H., Hamilton, T. S., Steggerda, F. R. and Bean, H. W. The chemical composition of the adult human body and its bearing on the biochemistry of growth. *J. Biol. Chem.*, 158: 625, 1945.
16. Armstrong, W. D., Johnson, J. A., Singer, L.,

LIENKE, R. I. and PREMER, M. L. Rates of transcapillary movement of calcium and sodium and of calcium exchange by the skeleton. *Am. J. Physiol.*, 171: 641, 1952.

17. THOMAS, R. O., LITOVITZ, T. A., RUBIN, M. I. and GESCHICKTER, C. F. Dynamics of calcium metabolism. I. Time distribution of intravenously administered radiocalcium. *Am. J. Physiol.*, 169: 568, 1952.
18. HANSARD, S. L., COMAR, C. L. and DAVIS, G. K. Effects of age upon the physiological behaviour of calcium in cattle. *Am. J. Physiol.*, 177: 383, 1954.
19. BRONNER, F., HARRIS, R. S., MALETSKOS, C. J. and BENDA, C. E. Studies in calcium metabolism. Effect of food phytates on calcium^{45} uptake in children on low-calcium breakfasts. *J. Nutrition*, 54: 523, 1954.
20. FREDERICKSON, J. M., HONOUR, A. J. and COPP, D. H. Measurement of initial bone clearance of Ca^{45} from blood in the rat. *Federation Proc.*, 14: 49, 1955.
21. DEJONG, B. P., TANAKA, G. and COPP, D. H. Unpublished data.
22. BAUER, G. C. H., CARLSSON, A. and LINDQUIST, B. Evaluation of accretion, resorption and exchange reactions in the skeleton. *Kgl. Fysiograf. Sällskap. Lund Förh.*, 25: 1, 1955.
23. BAUER, G. C. H. and CARLSSON, A. Metabolism of bone salt investigated by simultaneous administration of Ca^{32} and P^{32} to rats. *J. Bone & Joint Surg.*, 37B: 658, 1955.
24. BAUER, G. C. H., CARLSSON, A. and LINDQUIST, B. Bone salt metabolism in human rickets studied with radioactive phosphorus. *Metabolism*, 5: 573, 1956.
25. SINGER, L. and ARMSTRONG, W. D. Retention and turnover of radiocalcium by the skeleton of large rats. *Proc. Soc. Exper. Biol. & Med.*, 76: 229, 1951.
26. NORRIS, W. P. and KISIELESKI, W. Comparative metabolism of radium, strontium and calcium. *Cold Spring Harbor Symposium Quant. Biol.*, 13: 164, 1948.
27. AMPRINO, R. and ENGSTRÖM, A. Autoradiographic analysis of the distribution of labelled Ca and P in bones. *Sep. Experientia*, 8: 20, 1952.
28. SHERMAN, H. C. Chemistry of Food and Nutrition. New York, 1952. Macmillan Co.
29. HOWARD, J. E. Normal calcium and phosphorus transport and body fluid homeostasis. *Tr. Macy Conf. Metab. Interrelations*, 5: 11, 1953.
30. BRONNER, F. and HARRIS, R. S. Absorption and metabolism of calcium in human beings, studied with calcium^{45}. *Ann. New York Acad. Sc.*, 64: 314, 1956.
31. HOWARD, J. E., PARSON, W. and BIGHAM, R. S., JR. Studies on patients convalescent from fracture. III. The urinary excretion of calcium and phosphorus. *Bull. Johns Hopkins Hosp.*, 77: 291, 1945.
32. MCCANCE, R. A., WIDDOWSON, E. M. and LEHMANN, H. The effect of protein intake on the absorption of calcium and magnesium. *Biochem. J.*, 36: 686, 1942.
33. JOHNSTON, F. A., TREDWELL, C. and DIAO, E. Effect of previous calcium intake of four young men on amount retained from a low calcium diet. *Federation Proc.*, 15: 559, 1956.
34. LEICHSENRING, J. M., NORRIS, L. M., LAMISON, S. A., WILSON, E. D. and PATTON, M. B. The effect of level of intake on calcium and phosphorus metabolism in college women. *J. Nutrition*, 45: 407, 1951.
35. MCCANCE, R. A. and WIDDOWSON, E. M. Mineral metabolism of healthy adults on white and brown bread dietaries. *J. Physiol.*, 101: 44, 1942.
36. NICOLAYSEN, R. and NJAA, L. R. Investigations on the effect of phytic acid on the absorption of calcium in rats, pigs and men. *Acta physiol. Scandinav.*, 22: 246, 1951.
37. CHEN, P. S. and NEUMAN, W. F. Renal excretion of calcium by the dog. *Am. J. Physiol.*, 180: 623, 1955.
38. AUB, J. C., BAUER, W., HEATH, C. and ROPES, M. Studies of calcium and phosphorus metabolism. III. The effects of thyroid hormone and thyroid disease. *J. Clin. Investigation*, 7: 97, 1929.
39. COPP, D. H. Studies on the plasma clearance values of calcium. *Tr. Macy Conf. Metab. Interrelations*, 5: 147, 1953.
40. MCLEAN, F. C. and HASTINGS, A. B. Clinical estimation and significance of calcium-ion concentration in the blood. *Am. J. M. Sc.*, 189: 601, 1935.
41. HOPKINS, T., HOWARD, J. E. and EISENBERG, H. Ultrafiltration studies on calcium and phosphorus in human serum. *Bull. Johns Hopkins Hosp.*, 91: 1, 1952.
42. DENT, C. E. Discussion on the physiology and clinical disorders of the parathyroid glands. *Proc. Roy. Soc. Med.*, 46: 291, 1953.
43. HASTINGS, A. B. and HUGGINS, C. B. Experimental hypocalcemia. *Proc. Soc. Exper. Biol. & Med.*, 30: 458, 1933.
44. PATT, H. M. and LUCKHARDT, A. B. Relationship of a low blood calcium to parathyroid secretion. *Endocrinology*, 31: 384, 1942.
45. SAFFRAN, M. and DENSTEDT, O. F. The effect of intravenously injected citrate on the serum ionized calcium in the rabbit. *Canad. J. M. Sc.*, 29: 245, 1951.
46. SPENCER, H., GREENBERG, J., BERGER, E., PERRONE, M. and LASZLO, D. Studies on the effect of ethylenediaminetetraacetic acid in hypercalcemia. *J. Lab. Clin. Med.*, 47: 29, 1956.
47. COPP, D. H., FREDERICKSON, J. M. and DEJONG, B. Measurement of calcium mobilization in the dog. *Rev. Canad. Biol.*, 14: 244, 1955.
48. LEHMANN, J. A photoelectric micro method for the direct titration of calcium in serum with ethylenediaminetetraacetate. *Scandinav. J. Clin. & Lab. Investigation*, 5: 203, 1953.
49. ALBRIGHT, F. and REIFENSTEIN, E. C., JR. The Parathyroid Glands and Metabolic Bone Disease: Selected Studies. Baltimore, 1948. Williams & Wilkins Co.
50. GILMOUR, J. R. The Parathyroid Glands and Skeleton in Renal Disease. London, New York, 1947. Oxford University Press.
51. SNAPPER, I. Parathyroid hormone and mineral metabolism. *Bull. New York Acad. Med.*, 29: 612, 1953.
52. BARTTER, F. C. The parathyroids. *Ann. Rev. Physiol.*, 16: 429, 1954.
53. ALBRIGHT, F. and ELLSWORTH, R. Studies on the physiology of the parathyroid glands. I. Calcium

and phosphorus studies on a case of idiopathic hypoparathyroidism. *J. Clin. Investigation*, 7: 183, 1929.

54. Thomson, D. L. and Pugsley, L. I. On the mechanism of parathyroid hormone action. *Am. J. Physiol.*, 102: 350, 1932.
55. Collip, J. B., Pugsley, L. I., Selye, H. and Thomson, D. L. Observations concerning the mechanism of parathyroid hormone action. *Brit. J. Exper. Path.*, 15: 335, 1934.
56. Stewart, G. S. and Bowen, H. F. The parathyroid control of serum calcium independent of renal mediation. *Endocrinology*, 48: 568, 1951.
57. Selye, H. Mechanism of parathyroid hormone action. *Arch. Path.*, 34: 625, 1942.
58. Barnicot, N. A. The local action of the parathyroid and other tissues on bone in intracerebral grafts. *J. Anat.*, 82: 233, 1948.
59. Chang, H. Localized resorption of bone adjacent to parathyroid grafts. *Anat. Rec.*, 106: 266, 1950.
60. Talmage, R. V. and Elliott, J. R. Changes in extracellular fluid levels of calcium, phosphate and citrate ions in nephrectomized rats following parathyroidectomy. *Endocrinology*, 59: 27, 1956.
61. Frederickson, J. M., Thomas, W. D. S. and Copp, D. H. To be published.
62. Copp, D. H. and Moghadam, H. To be published.
63. Bloom, W., Bloom, M. A. and McLean, F. C. Calcification and ossification. Medullary bone changes in the reproductive cycle of female pigeons. *Anat. Rec.*, 81: 443, 1941.
64. Urist, M. R., Budy, A. M. and McLean, F. C. Endosteal-bone formation in estrogen-treated mice. *J. Bone & Joint Surg.*, 32A: 143, 1950.
65. Budy, A. M., Urist, M. R. and McLean, F. C. The effect of estrogens on the growth apparatus of the bones of immature rats. *Am. J. Path.*, 28: 1143, 1952.
66. Ackerman, P. G., Toro, G., Kountz, W. B. and Kheim, T. The effect of sex hormone administration on the calcium and nitrogen balance in elderly women. *J. Geront.*, 9: 450, 1954.
67. Reifenstein, E. C., Jr. and Albright F. The metabolic effects of steroid hormones in osteoporosis. *J. Clin. Investigation*, 26: 24, 1947.
68. Walker, D. G., Simpson, M. E., Asling, C. W. and Evans, H. M. Growth and differentiation in the rat following hypophysectomy at 6 days of age. *Anat. Rec.*, 106: 539, 1950.
69. Asling, C. W., Simpson, M. E. and Evans, H. M. Effects of pituitary factors and of thyroxin on skeletal morphogenesis in the rat. *Tr. Macy Conf. Metab. Interrelations*, 3: 125, 1951.
70. Becks, H., Simpson, M. E., Evans, H. M., Ray, R. D., Li, C. H. and Asling, C. W. Response to pituitary growth hormone and thyroxin of the tibias of hypophysectomized rats after long postoperative intervals. *Anat. Rec.*, 94: 631, 1946.
71. Talmage, R. V., Dodds, B. F. Comparative study of some effects of administration of dihydrotachysterol and calciferol to rats. *Endocrinology*, 57: 236, 1955.
72. Zetterstrom, R. and Winberg, J. Primary vitamin D refractory rickets. II. Metabolic studies during treatment with massive doses of vitamin D. *Acta paediat.*, 44: 45, 1955.
73. Cohn, W. E. and Greenberg, D. M. Studies in mineral metabolism with the aid of artificial radioactive isotopes. I. Absorption, distribution and excretion of phosphorus. *J. Biol. Chem.*, 123: 185, 1938.
74. Feaster, J. P., Shirley, R. L., McCall, J. T. and Davis, G. K. P^{32} distribution and excretion in rats fed vitamin D free and low phosphorus diets. *J. Nutrition*, 51: 381, 1953.
75. Carlsson, A. The effect of vitamin D on the absorption of inorganic phosphate. *Acta physiol. Scandinav.*, 31: 301, 1954.
76. Rehm, P., and Winters, J. C. The effect of ferric chloride on the utilization of calcium and phosphorus in the animal body. *J. Nutrition*, 19: 213, 1940.
77. Street, H. R. Influence of aluminum sulfate and aluminum hydroxide upon the absorption of dietary phosphorus by the rat. *J. Nutrition*, 24: 111, 1942.
78. Harrison, H. E. and Harrison, H. C. Renal excretion of inorganic phosphate in relation to the action of vitamin D and parathyroid hormone. *J. Clin. Investigation*, 20: 47, 1941.
79. Copp, D. H. Unpublished data.
80. Crawford, J. D., Osborne, M. M., Jr., Talbot, N. B., Terry, M. L. and Morrill, M. F. The parathyroid glands and phosphorus homeostasis. *J. Clin. Investigation*, 29: 1448, 1950.
81. Talmage, R. V., Kraintz, F. W., Frost, R. C. and Kraintz, L. Evidence for a dual action of parathyroid extract in maintaining serum calcium and phosphate levels. *Endocrinology*, 52: 318, 1953.
82. Stoerk, R. C. and Silber, R. H. Parathormone in renal reabsorption of phosphate. *Lab. Investigation*, 5: 213, 1956.
83. Rubin, B. L. and Dorfman, R. I. Bioassay of parathyroid hormone. *Proc. Soc. Exper. Biol. & Med.*, 83: 223, 1953.
84. Reifenstein, E. C., Jr., Kinsell, L. W. and Albright, F. Observations on the use of the serum phosphorus level as an index of pituitary growth hormone activity; the effect of estrogen therapy in acromegaly. *Endocrinology*, 39: 71, 1946.
85. Handler, P. and Cohn, D. V. The question of two or more forms of phosphate in plasma. *Tr. Macy Conf. Metab. Interrelations*, 5: 339, 1953.
86. Zucker, T. F., Hall, L. and Young, M. Growth and calcification on a diet deficient in phosphate but otherwise adequate. *J. Nutrition*, 22: 139, 1941.
87. Day, H. G. and McCollum, E. V. Mineral metabolism, growth and symptomatology of rats on a diet extremely deficient in phosphorus. *J. Biol. Chem.*, 130: 269, 1939.
88. Coleman, R. D., Becks, H., Kohl, F. van N. and Copp, D. H. Skeletal changes in severe phosphorus deficiency of the rat. I. Tibia, metacarpal bone, costochondral junction, caudal vertebra. *Arch. Path.*, 50: 209, 1950.
89. Copp, D. H., Hamilton, J. G., Jones, D. C., Thomson, D. M. and Cramer, C. F. The effect of age and low phosphorus rickets on calcification and the deposition of certain radioactive metals in bone. *Tr. Macy Conf. Metab. Interrelations*, 3: 226, 1951.
90. Copp, D. H. To be published.

Clinico-pathologic Conference

Pyuria, Gross Hematuria, Convulsions and Possible Nephrotic Syndrome

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient (No. 267247), a fifty-four year old Negro housewife, was admitted to Barnes Hospital for the first time on February 13, 1956, in a state of collapse following a convulsive episode. She was readmitted on May 3, 1956 and died on May 27, 1956.

The patient was well until about 1951 when she had severe dysuria for one week which cleared spontaneously. During the next few years she had several episodes of aching in her flanks, unassociated with other symptoms. She was first seen at the Washington University Clinic in 1952 for an abscess on her arm. At this time she was noted to have a blood pressure of 150/95 and slight cardiac enlargement. Urinalysis revealed "trace protein" and "full field" of red and white blood cells. She was not seen again until November, 1955, when she returned for treatment of a small ulcer on her leg. She was noted to have 4 plus proteinuria and 8 to 15 red cells per high powered field. An electrocardiogram was normal. Roentgenogram of her chest revealed left ventricular enlargement. About four months prior to her first admission there was an "uneasiness" in her stomach followed by recurrent vomiting for one week and nausea which persisted intermittently until admission. Two months prior to admission pedal edema developed which was followed by periorbital edema, both of which progressed. She also had slight exertional dyspnea which did not become severe until one month prior to admission when orthopnea also developed. Two weeks prior to admission, she was seen in the Medicine Clinic where notable findings were generalized edema, a blood pressure of 180/100, cardiomegaly, hydrothorax, ascites and marked dependent edema. The venous pressure was 220 mm. saline, the circulation time (decholin®) was sixteen seconds. Urinalysis showed 3 plus proteinuria, and many white blood cells; culture of the urine revealed no growth. The hemoglobin was 10.2 gm. per cent, the non-protein nitrogen 38 mg. per cent. Seven days prior to admission the patient began to spend most of her time in bed because of malaise and severe dyspnea. On the day of admission she collapsed in bed and clonic activity of her extremities developed but she did not lose sphincter control or become cyanotic. Following this episode she was confused and was brought to the Emergency Room.

Her general health and strength had been excellent in the past. She had had no operations, previous hospitalizations or serious illnesses. She was gravida IX, para IX without any complications. She was two years postmenopausal. There was no previous history of cardiac disease or gastrointestinal symptoms. Her family history was not contributory.

Physical examination revealed the patient's temperature to be 37.7°C., pulse 120, respiration 24, blood pressure 205/110. She was obese, edematous and somnolent. There was periorbital edema. The pupils were round, regular, equal and reacted to light. There was a moderate increase in the arteriolar light reflex, but no other abnormalities of the fundi were observed. The ears, nose and throat were normal. The neck was supple. The neck veins were not distended. The thyroid was not enlarged. There was dullness and decreased tactile fremitus bilaterally at the lung bases with fine inspiratory rales superior to the dullness. The left border of cardiac dullness and point of maximal impulse was 12 cm. to the left of the midsternal line in the fifth intercostal space. A medium pitched,

blowing, grade 2, apical, systolic murmur was present. There was no friction rub or gallop rhythm. The abdomen was distended with ascites; however, no organs or masses were ballotable. Slight bilateral costovertebral angle tenderness was noted. There was a small superficial ulcer on the left labia majora. Pelvic and rectal examinations were normal. The skin was dry and somewhat coarse. There was marked pitting edema of the legs and moderate presacral edema. Muscle tone was fair and the tendon reflexes were symmetrically hyperactive, There were no pathologic reflexes.

The laboratory examinations were as follows: red blood cells 2.65 million per cu. mm.; hemoglobin 7.0 gm. per cent; hematocrit 22 per cent; white cell count 7,000 per cu. mm.; differential: 78 per cent segmented forms, 2 per cent band forms, 18 per cent lymphocytes, 2 per cent monocytes. The platelets appeared adequate. The red blood cells appeared normocytic and normochromic. The reticulocyte count was 2.1 per cent. Mean corpuscular volume 83 cubic microns; mean corpuscular hemoglobin 26 gamma gamma; mean corpuscular hemoglobin concentration 31 per cent. Urinalysis (catheterized specimen): specific gravity 1.011; reaction 6; protein 3 plus; sugar negative; bilirubin negative; urobilinogen positive in 1 to 2 but negative in 1 to 4 dilutions. Microscopic examination of the sediment revealed large numbers of hyaline and granular casts; 50 to 100 red blood cells per high powered field; 10 to 15 white blood cells with some clumps per high powered field. Methylene blue stain showed no bacteria. Quantitative urine protein studies revealed an excretion of 3 gm. of protein per liter of urine. The stool was liquid, yellow in color, and was negative by guaiac test. Cardiolipin was negative. Non-protein nitrogen was 33 mg. per 100 ml., fasting blood sugar 65 mg. per cent, 2 hour postprandial blood sugar 80 mg. per cent, sodium 141.9 mEq./L., potassium 5.5 mEq./L., chloride 125 mEq./L., CO_2 16.5 mEq./L., calcium 9 mg. per cent, phosphorus 4.7 mg. per cent, total protein 4.3 gm. per cent, albumin 1.7 gm. per cent, globulin 2.6 gm. per cent, cholesterol 267 mg. per cent, and bromsulphalein 2 per cent retention in forty-five minutes. Total serum bilirubin was less than 0.8 mg. per cent, cephalin-cholesterol flocculation negative, thymol turbidity 3.6 units, direct Coombs' test negative, and phenolsulfonphthalein 3 per cent excretion in two hours. Preparations for L.E. cells were negative three times. Roentgenograms of the chest revealed left ventricular enlargement, left lower lobe pneumonitis and bilateral pleural effusions. An electrocardiogram on February 6, 1956 was within normal limits. Culture of the blood was negative. Culture of urine revealed a moderate growth of coagulase negative micrococcus albus. Cultures of throat and sputum grew out a mixed flora of Neisseria catarrhalis, alpha hemolytic streptococcus and coliform organisms. Circulation time (decholin) was ten seconds, and the venous pressure was 175 mm. of saline. Ascitic fluid obtained by paracentesis showed a specific gravity of 1.004, protein 0.7 gm. per cent, cells without acid 30, with acid 24. Sternal marrow aspiration revealed normal cellularity and adequate megakaryocytes. There was slight normoblastic hyperplasia but otherwise the bone marrow was normal.

While in the hospital the patient was given a diet which contained 0.5 gm. sodium chloride. She was digitalized but no attempt was made to lower the patient's blood pressure which stayed at about 200/105. One injection of a mercurial diuretic caused no diuresis. Two paracenteses which removed a total of 3,400 cc. of fluid resulted in a weight loss from 132 to 120 pounds. The patient's weight then stayed at about 120 pounds throughout the remainder of the hospitalization. From the eighth to the twenty-first hospital day, 120 units of ACTH gel were administered daily. The electrolytes were checked frequently and showed little change. The non-protein nitrogen, which had risen to 55 mg. per cent prior to ACTH therapy, rose to 84 mg. per cent. The hemoglobin was 7.1 gm. per cent; the white cell count rose to 21,000 per cu. mm. with a slight left shift. There was no fever or infection at this time. No diuresis occurred. On the twenty-eighth hospital day, the temperature rose from the patient's normal level of 36.8° to 38.2°C. Physical examination revealed no abnormalities except for slight costovertebral angle tenderness. Radiologic examination of the chest was unchanged from that of February 6, 1953. The urine sediment revealed a few hyaline, finely and coarsely granular casts. Rare renal failure casts were seen. Methylene blue stain showed very few bacteria. A culture of the urine revealed growth of coagulase positive, Micrococcus aureus which was moderately sensitive to tetracycline and chloramphenicol, and resistant to erythromycin.

Tetracycline therapy, 0.5 gm. every six hours, was started and continued until discharge. The patient became afebrile on the thirty-second hospital day, but urinalysis continued to show many white cells and culture revealed a moderate growth of coagulase negative mixed Micrococcus albus and aureus.

On the twenty-eighth hospital day blood chemical determinations were: non-protein nitrogen 60 mg. per cent, sodium 130.9 mEq./L., potassium 5.8 mEq./L., CO_2 19.2 mEq./L., chloride 103 mEq./L., total protein 4.0 gm. per cent, albumin 2.5 gm. per cent, globulin 1.5 gm. per cent. During the next seven days, the fluid intake averaged 2,200 cc. daily and the urine output averaged 800 cc. daily. On the thirty-fifth hospital day, the non-protein nitrogen was 112 mg. per cent, sodium 113.6 mEq./L., potassium 6.3 mEq./L., CO_2 12.4 mEq./L., chloride 90 mEq./L. The fluid intake was then restricted to 1,500 cc. daily and enteric coated sodium chloride tablets, 3 gm. daily, were given. By the forty-second hospital day the non-protein nitrogen was 116 mg. per cent, sodium 136.7 mEq./L., potassium 6.8 mEq./L., CO_2 15.5 mEq./L., chloride 102 mEq./L., calcium 7.0 mg. per cent and phosphorus 7.7 mg. per cent.

Because the hemoglobin had fallen to 5.8 gm. per cent, the patient was given 2 units of packed red cells through a venous pressure set. The venous pressure did not rise above 130 mm. of saline. The hemoglobin increased to 8.3 gm. per cent. Although her condition had not improved, the patient was discharged on the forty-fourth hospital day at her family's request. Discharge medications were gitaligin,® basaljel® and chlorpromazine.

During the interval of one month before readmission, the patient was seen at the clinic on two occasions and although hypertension, pleural effusion, ascites, and dyspnea persisted, her condition did not deteriorate. She took her medications regularly. The morning of admission she complained of a severe generalized headache. Shortly thereafter, she became semi-comatose and had three grand mal seizures, in each of which her head was turned to the left. She was brought to the emergency room in a comatose state and admitted for her final hospitalization from May 3, to May 27, 1956.

Physical examination revealed the temperature to be 38.5°C., pulse 130, respiration 20, blood pressure 200/90, weight 105 pounds. The patient was comatose but in no respiratory distress, lying flat in bed. The pupils were round, regular and equal, and reacted to light. The fundal vessels showed moderate arteriovenous compression, a few hard exudates, but no hemorrhages or papilledema. Examination of the ears, nose and throat revealed no abnormalities. The neck was supple. Dullness and decreased breath sounds were detected at the lung bases. There were a few fine rales at the right base. The point of maximum impulse was in the sixth left intercostal space at the anterior axillary line. The cardiac examination was otherwise unchanged. There was moderate ascites. There were no palpable organs or masses. There was slight pretibial edema. Except for her comatose state the neurologic examination was unchanged from the previous admission. There were no pathologic reflexes.

Laboratory studies at this time were: red cell count, 2.68 million per cu. mm.; hemoglobin 7.7 gm. per cent, packed cell volume 22 per cent, white blood count 14,450 per cu. mm.; differential: 89 per cent segmented neutrophils, 1 per cent band forms, 9 per cent lymphocytes, 1 per cent monocytes. The platelets appeared adequate. Mean corpuscular volume, 80 cubic microns; mean corpuscular hemoglobin 25 gamma gamma; mean corpuscular hemoglobin concentration, 35 per cent. Urinalysis: specific gravity 1.011, reaction 5.5, protein 4+, sugar negative. Microscopic examination of the sediment revealed many hyaline and granular casts, 8 to 10 red cells and 10 to 14 white cells per high powered field. The stool was brown; the guaiac test was positive. Non-protein nitrogen was 50 mg. per cent, sodium 141.9 mEq./L.; potassium 6.5 mEq./L.; CO_2 15.8 mEq./L.; chloride 110 mEq./L.; fasting blood sugar 112 mg. per cent; calcium 9.2 mg. per cent; phosphorus 2.1 mg. per cent; total serum protein 5 gm. per cent; albumin 2.1 gm. per cent; globulin 2.9 gm. per cent; and cholesterol 314 mg. per cent. Two L.E. tests were negative. A non-standard radiographic examination of the chest revealed no gross abnormalities. Radiographic examination of the skull was negative; the pineal was not calcified. An electroencephalogram showed bifrontal slow activity which was interpreted as "sign of continuous disorder in the tracing." There were also "runs of convulsoid activity more diffusely distributed." There were no lateralizing signs. The record was consistent with convulsive etiology on a diffuse organic basis with the following possibilities to be con-

sidered: (1) a deep frontal lesion or (2) metabolic or electrolyte alteration. The electrocardiogram revealed an abnormal form of ventricular complex compatible with digitalis effect. Cultures of the blood were sterile. Cultures of the throat grew out alpha hemolytic Streptococcus and Neisseria catarrhalis. Cultures of the urine grew a confluent, mixture of Micrococcus aureus and Proteus.

The patient was treated with digilanid intramuscularly and tetracycline orally. A lumbar puncture performed on admission showed an initial pressure of 160 mm. spinal fluid and, after the removal of 8 cc., a final pressure of 120 mm. There were no cells. The protein was 37 mg. per cent, the sugar 105 mg. per cent. The colloidal gold test and Wassermann reaction were normal. During the first hospital day there was occasional clonic activity on the left side of the body, but this stopped shortly after the patient was given phenobarbital intramuscularly and dilantin® by stomach tube. By the third hospital day, she was improved; she took food and medications orally, but some confusion and lethargy remained. The stools were persistently positive for occult blood and the urine showed gross hematuria. The prothrombin time was 80 per cent; the bleeding time one and a half minutes; clotting time six minutes; the clot retraction, good in two hours, the Rumple-Leede test was negative. Complete radiologic examination of the gastrointestinal tract showed only a diverticulum of the distal esophagus and of the duodenum. Ascites and osteitis condensans iliae were also noted. On the eighth hospital day the red cell count was 1.9 million per cu. mm.; the hemoglobin 5.8 gm. per cent, the packed cell volume 18 per cent. The patient received 500 ml. of whole blood which increased the hemoglobin to 9 gm. per cent. On the twelfth hospital day she suddenly had three more grand mal seizures. The neurologic examination revealed a transiently pathologic left toe sign. The non-protein nitrogen was 96 mg. per cent, sodium 139.4 mEq./L., potassium 6 mEq./L., CO_2 17.5 mEq./L., chloride 116 mEq./L. After these seizures the patient became less responsive and was disoriented as to time and place. Repeat electroencephalogram revealed "a decrease in the per cent time of intermediate slow waves and the frontal lead combinations to be significantly reduced." Cystoscopy was performed on the fifteenth hospital day. The findings were a bloody discharge from the left ureter and a purulent discharge from the right ureter. A left retrograde pyelogram showed a large dilated collecting system compatible with multiple renal abscesses, tumor or polycystic kidney. On the sixteenth hospital day the temperature rose to 38.8°C., and a mild leukocytosis developed. The urine continued to be grossly bloody. Urine culture grew out a confluent mixture of coliform organisms and Micrococcus albus. Culture of the blood revealed coliform organisms. Chloramphenicol 200 mg. intramuscularly every six hours was added to the tetracycline therapy. The patient continued to be obtunded; the leukocytosis persisted; and the temperature ranged from 37.4 to 39.8°. Repeated neurologic examinations failed to demonstrate lateralizing findings. The patient died quietly on the twenty-fourth hospital day.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: Let us consider first the problem of this patient's anemia. It is of interest that during the two weeks preceding her admission, the patient's hemoglobin value had fallen from 10.2 gm., as noted in the clinic, to 7 gm. on admission to the hospital. A reticulocyte count shortly after admission was 2.1 per cent. The mean corpuscular hemoglobin concentration was 31 and the bone marrow showed slight normoblastic hyperplasia. As you all know, chronic azotemia is certainly a cause of anemia and may have been a contributory factor in this patient. Dr. Philip Loge did some studies several years ago that may be pertinent here. These studies were concerned with red cell survival times as measured by the Ashby technic in patients with anemia, kidney disease, and some degree of azotemia. In one group of patients, normal blood cell survival times were obtained despite the anemia. In another group, with more severe anemia and more marked azotemia, very significantly shortened red cell survival times were observed. So we may say that in patients who have severe azotemia, with accompanying severe anemia, there is often a hemolytic component contributing to the anemia; whereas in mild azotemia one does not anticipate a hemolytic component. Dr. Loeb would you discuss other factors which may have contributed to the anemia in this particular case?

DR. VIRGIL LOEB: There are many factors which may have been responsible for the anemia and I do not believe we can be very specific as to the actual cause. She certainly had impaired

renal function and, as was pointed out, anemia is quite commonly seen in renal disease although a significant hemolytic component may not become manifest until severe azotemia occurs. She had hypoproteinemia, which might be a contributing factor to defective hemoglobin synthesis. Infection may be responsible for anemia. She certainly had a chronic urinary tract infection so that the possibility of her having had a renal abscess will have to be considered in the discussion. The possibility of a chronic septicemia also has to be entertained. Furthermore, she had evidence of chronic blood loss from the genitourinary tract; except for one isolated observation when red cells were absent from her urine, and on many occasions there was gross hematuria. Blood was also noted in her stool so that another significant source of blood loss could have been the gastrointestinal tract. Finally we are told that she had had nine pregnancies all of which may well have depleted the body of iron. According to the protocol the corpuscular constants on this patient were normochromic and therefore a significant degree of iron deficiency presumably did not play much of a role but certainly with the infection, the renal disease, and the hypoproteinemia, supplemented by the chronic blood loss I think we have sufficient reasons to anticipate that such a patient would be anemic.

DR. REINHARD: She did actually have a very mild or borderline hypochromic anemia. I think it might be worth while here to comment on the problem of transfusion in a patient of this sort. There is always much discussion on the wards and on the clinical services because everybody is afraid of provoking a severe hemolytic transfusion reaction in this sort of patient. Dr. Loeb, can a transfusion be given to these people safely and if so what do you do to avoid transfusion reaction?

DR. LOEB: I think we might start by saying that you can't give a transfusion to any patient with complete safety. There is always a calculated risk in blood transfusion, but most individuals with adequate kidney function are able to clear the mild degree of hemoglobinemia that occurs following the transfusion of stored blood. However, in a patient with renal disease, one is obviously up against a problem because of the compromised kidneys. There are various ways to give a transfusion to an individual with perhaps greater caution than is ordinarily exercised. Packed red cells may be administered, sometimes through a venous pressure set, if a patient is in circulatory failure, or if one has any reason to anticipate that he might go into circulatory failure, or if one is interested simply in giving red blood cells to the individual. This procedure was used here. Recently people have looked upon the technic of washing red cells as a panacea for the prevention of transfusion reaction but I think a word of caution is justified. Actually when one washes red cells, all one attempts to do is remove the last traces of plasma. If there are antibodies in the donor's plasma to which the recipient's cells may be sensitized, then perhaps it is rational to remove all the antibody by washing. This is a very rare circumstance, however. If the patient is sensitive to plasma, and I mean by this non-specifically sensitive—that is, that a febrile reaction will develop following injection of pooled plasma without regard to type—then it may be necessary to wash the red cells repeatedly in order to get rid of any trace of plasma protein that might be present in the infused blood. I suppose washing cells might be considered also if one is worried about hyperkalemia. But I think it is important to realize that in washing red blood cells, one does undoubtedly traumatize the cells. It is a heroic experience for the red cells to be taken out of the body, have the plasma removed, be resuspended in saline, spun down again, the saline removed and a new infusion of saline mixed with the cells for a total of at least three times. This process may take several hours during which time, it is absolutely essential that the blood be maintained sterile and kept at optimal storage temperature which is between 4° and 8°C. Now if one traumatizes the red cells by washing, then it seems to me it is only reasonable to assume that following infusion of such washed cells one might actually do more damage than by giving simply the packed cells. If the washed cells are osmotically or mechanically more fragile after washing, they may well hemolyze following their infusion into the recipient and result in further elevation of serum potassium and hemoglobinemia. Recently Drs. Chaplin and Brittingham here have done some interesting preliminary studies that may give another indication for washing red cells, namely to remove white cells and platelets which may be responsible for some reactions. But I believe, unless there is a good reason to suspect that there is some inherent potentially dangerous substance in the plasma, one accomplishes very little by washing the red

cells and one may endanger the recipient in terms of jeopardizing already damaged kidneys by giving potentially traumatized red cells.

DR. REINHARD: The next problem I would like to take up is the pathogenesis of the patient's generalized edema or anasarca. We have two possibilities that we have to consider: (1) the nephrotic syndrome of the mixed variety, that is nephrosis plus renal hypertension and azotemia or, (2) nephritis with renal hypertension and congestive heart failure. It is important for us to decide which of these the patient had if we are to fit this very confusing case together. Dr. Bricker, which of these possibilities do you think we are dealing with here?

DR. NEAL BRICKER: Unfortunately I don't think that available data allow us to distinguish absolutely between the two mechanisms. We can't really substantiate the diagnosis of the nephrotic syndrome in this patient, if we list as our criteria for diagnosis (1) a decreased plasma albumin concentration, marked albuminuria, a hypercholesterolemia, hyperlipemia and/or lipiduria and anasarca. People with the nephrotic syndrome usually have over 6 gm. of protein in the urine during a twenty-four hour period. In this patient, we know only that in one twenty-four hour urine sample, the protein concentration was 3 gm./L., but we do not know the twenty-four hour volume on that day.

DR. REINHARD: As far as we can tell from the chart the urinary outputs throughout that period were recorded as between 800 and 1,000 cc. per day. These figures are always of course subject to question.

DR. BRICKER: The cholesterol values ranged from high normal to one value which was over 300 but nevertheless, the majority of values I believe were in an equivocal range. The hardest thing to explain on the basis of congestive heart failure is the hypoalbuminemia and this was definite and persistent. She did have congestive heart failure. With congestive heart failure and hypoalbuminemia, the distribution of her edema with ascites and pleural effusions could well have occurred. I think the chances are perhaps 85 per cent in favor of a nephrotic syndrome.

DR. REINHARD: It is well worth pointing out that if we did have information about the twenty-four hour protein output of urine it would be of great value in deciding this rather crucial point, but that information is unfortunately not available. Dr. Smith, do you have anything to add about this patient's congestive failure? Would you agree that she had congestive failure? The patient's venous pressure was 220 but the decholin circulation time was normal, sixteen seconds.

DR. JOHN SMITH: There was probably an element of congestive failure, I imagine. There was marked water overload and the venous system was impounded considerably which would represent an inability of the heart to move all this volume.

DR. REINHARD: It is appropriate now to attempt to decide what kind of renal disease was present. I'd like to see the pyelograms Dr. Powers.

DR. WILLIAM POWERS: The kidney outlines cannot be visualized and the films have a marked overcast on them which is due to the tremendous amount of abdominal fluid. However on a gastrointestinal series performed about four months before this examination, both kidneys appeared to be normal in size and external configuration. A retrograde pyelogram was attempted and following non-visualization of the kidney, presumably due to the dye escaping back down the ureter, a bulb was put into the distal ureter and dye forced in a retrograde manner. Retrograde pyelography of the left kidney shows it to be very abnormal. The radiology department equivocated considerably about the absolute diagnosis. There is a defect in the mid-portion of the pelvis of the kidney; there is irregularity and destruction of a portion of the mucosa of the proximal ureter and the distal pelvis; there are several filling defects within the pelvis, and there is a filling defect within one of the major calyces. Marked irregularity and dilatation of the calyces with a filling defect extending out from the calyx in the lower portion of the kidney is also seen. These findings are suggestive of tuberculosis except that there is no atrophy of the kidney and there is relatively little involvement of the ureter. The lesion might suggest a tumor within the renal structure but it would have to be a very diffuse tumor. I think a more reasonable dignosis would be that the kidney has multiple sites of infection within it, probably with abscesses, which are in communication with the renal pelvis and the renal collecting system. A renal pelvic tumor could explain the entire picture with clotting of blood and infection. My preference would be for multiple abscesses within the kidney. There was no contrast examination performed on the opposite right kidney.

DR. REINHARD: We may as well go ahead and see the roentgenogram of the chest too.

DR. POWERS: Fortunately we have roentgenograms of the chest going back to 1952. There is relatively little change in the size of the heart. The heart shows generalized enlargement in both the transverse and anteroposterior diameters. There is at this time pleural effusion bilaterally, with effusion extending up along both costophrenic angles; the diaphragms are both somewhat elevated presumably because of the tremendous amount of fluid within the abdomen. The bronchus in the left lower lobe can be seen relatively well and there is a patchy infiltration in the left lower lobe best interpreted as pneumonitis. There is possibly some pulmonic vascular congestion. The vessels are somewhat enlarged, and several of the roentgenograms show the azygos vein considerably enlarged. The pulmonary vessels were not tremendously dilated as seen in severe congestive failure, however.

DR. REINHARD: Dr. Powers, the diagnosis of polycystic kidneys with superimposed pyelonephritis was suggested in the chart. Did the size of the kidneys help you in your report?

DR. POWERS: Well, yes, I think these kidneys were smooth in outline, not lobular, and not particularly enlarged in size.

DR. REINHARD: Nine days before the patient died, a cystoscopy was performed. Reddish discharge was observed coming from the left ureter, and a purulent discharge was observed coming from the right ureter. Now Dr. Royce, considering not only the pyelograms but all the other data we have on this patient, what kind of renal disease do you think this patient had?

DR. ROBERT ROYCE: There are a number of possibilities. I think most of them have already been mentioned. There are a number of things which would make it almost impossible to make a positive diagnosis right now, because we are seeing a patient that was first examined urologically when she was in a terminal condition. She did have several very salient features in her course which I think should be borne in mind. One is that she had persistent blood and pus in her urine from the time she was first seen in the clinic in 1952. She had at that time and until the last admission, no recorded sepsis that I could find. She also had negative cultures in the clinic when she had pus and blood in her urine. At least the first one or two methylene blue stains were negative. This group of findings sounds more like acid-fast infection or a tumor. It is possible, of course, to have a stone with local necrosis and no sepsis or bacteria. However, from the roentgenograms alone I rather suspect that she does have multiple abscesses of the kidney. I don't know what the nature of the abscesses was, but, even with no evidence of pulmonary tuberculosis I would still be a little suspicious of a tuberculous infection. She had bilateral disease and it is not unusual for renal tuberculosis to be associated with hematuria, particularly when there is pus with no bacteria. I believe the cultures were a little equivocal here. Of the bacteria that were listed, I believe the micrococcus, in particular, might have been a contaminant.

DR. REINHARD: Dr. Wattenberg, do you have anything to add? I wish you would also comment on the possibility that this woman might have had two types of renal disease. Could she have had a long standing chronic pyelonephritis and a superimposed process causing a very acute, terminal picture with the bizarre pyelogram?

DR. WATTENBERG: The history would lead one to think that she had a long standing infection of the kidneys, because of the pus and blood cells. The red cells were found back in her early history. I think perhaps she did have a long standing pyelonephritis, the cause not being determined as yet. Perhaps in the terminal state some type of toxic nephritis or nephrosis developed. I still think we have to bear in mind that she could have had tuberculosis for a long time because the pyelograms suggest it and the history with a normal white count and no fever would fit in.

DR. REINHARD: Now Dr. Recant, if we assume that the patient did have a nephrotic syndrome rather than nephritis and cardiac failure alone as the cause of the edema, what are the types of renal lesions we would have to consider? In other words, what types of renal disease produce the nephrotic syndrome of the impure type? I would particularly like you to emphasize what is the renal lesion that characterizes nephrosis. Is there any one common denominator of the renal lesions that cause nephrosis?

DR. RECANT: There are a variety of etiologies associated with the nephrotic syndrome. These include chronic glomerular nephritis, lupus erythematosus, amyloidosis, involvement of the renal veins by bilateral thrombosis, drug induced syndromes, and a few cases have been reported of secondary syphilis with an associated

nephrotic syndrome. With respect to the common denominator in the pathogenesis of this renal lesion, it seems clear that the glomerulus appears to be the organ or the site of attack. This fact is not always clearly demonstrable on the usual routine sections but in most studies one can demonstrate changes in the basement membrane. I failed to mention the Kimmelsteil-Wilson syndrome as another cause of this syndrome. The major question here is the one Dr. Bricker commented on, namely did she have a nephrotic syndrome? If she did not, I think we can deal with the case much more simply. If she did, none of these diseases fits easily. The fact that she did have recurrent infection perhaps is the only one that would suggest amyloidosis but that seems highly improbable.

DR. REINHARD: Isn't it true that in most conditions that cause nephrosis the kidneys tend to be large so that, if this patient had nephrosis, the normal size of the kidneys would be unusual.

DR. REGANT: I think that is essentially true.

DR. REINHARD: Dr. Bricker, one other diagnosis ought to be mentioned, disseminated lupus. Many L.E. preparations were sent to the laboratory and all were negative. Do consistently negative L.E. preparations rule out disseminated lupus with any degree of certainty?

DR. BRICKER: I do not believe they rule out the diagnosis of lupus. Kark has recently described a patient with lupus who initially had positive L.E. preparations with a renal lesion producing the nephrotic syndrome; but as the disease progressed the L.E. phenomenon became negative and remained negative thereafter. In the experience of most observers, however, the L.E. test does not revert to negative after once being positive.

DR. REINHARD: Dr. Bricker, there are certain blood chemical findings listed in the protocol which one would certainly not expect in nephrosis. These include those of hyperchloremic acidosis, and a low normal serum phosphorus (as low as 2.1 mg. per cent) at times when the patient apparently had severe and progressive renal failure. I would have expected the serum phosphorus to be very high. Would you discuss these changes?

DR. BRICKER: The observations are, to say the least, intriguing. When the patient was first examined chemically she had a definite hyperchloremic acidosis. Her azotemia then was only modest. One would wonder, therefore, whether or not she presented some of the manifestations of renal tubular acidosis without severe glomerular insufficiency early in her course. Certainly this syndrome would be compatible with an etiologic diagosis of pyelonephritis. Later she became more azotemic due to a process which we don't fully understand. At the time of discharge from the hospital (following her first admission) she was severely uremic. However, when she was at home, her glomerular filtration rate inexplicably increased as is evidenced by a marked fall in the non-protein nitrogen concentration and by the drop in the phosphorus from 7 mg. per cent or thereabouts to 2.1 mg. per cent. The serum phosphorus level does not generally become elevated until the glomerular filtration rate drops below 30 ml. per minute. Hence her glomerular filtration rate must have been extremely low. It is possible to explain some of the fall in phosphorus (and corresponding rise in calcium) on the basis of the increased filtration rate. But this change alone cannot produce hypophosphatemia so that again one wonders whether or not the increased filtration rate unmasked an underlying renal tubular acidosis.

DR. REINHARD: But as you have already stated, Dr. Bricker, you think there is roughly an 85 per cent chance that this patient did have a nephrotic syndrome and that it should be so classified. If that is the case, I gather from the discussion we have had so far that you would have to postulate that the patient had two types of renal disease. One to account for this bizarre pyelogram, perhaps a chronic pyelonephritis, perhaps a renal tuberculosis, and then there is some other renal lesion to account for the nephrosis. Is that correct?

DR. BRICKER: Yes.

DR. REINHARD: Would you like to state what you think would be the most likely cause of the nephrotic syndrome?

DR. BRICKER: I would have to list two or three possibilities, and I don't think I could distinguish between them. I think one possibility is as follows: When first seen in 1952 this patient had latent chronic glomerulonephritis, with occult hematuria as a manifestation. When she came to the hospital on her first admission she may have suffered an acute exacerbation of chronic glomerulonephritis with resultant azotemia, oliguria and hyperkalemia. Finally this acute exacerbation subsided in part and was then followed by the nephrotic syndrome. Other possibilities, however, must be mentioned. Systemic lupus has already been considered. We can

neither rule it out, nor rule it in. Amyloidosis could be the etiologic basis of a nephrotic syndrome and I think would be more plausible if she had renal tuberculosis. The other possibility which I would like to mention is bilateral renal vein thrombosis. The fact that she had flank pain recorded in 1952 and thereafter, the fact that she did have a considerable amount of hematuria, and the fact that she seemed to have a disproportionate amount of ascites, would indicate that renal vein thrombosis might have to be considered.

DR. REINHARD: Dr. Bricker, I would like you to tell us very briefly what your experience has been at Peter Bent Brigham Hospital in the therapy of nephrosis with massive doses of cortisone. Are they really significantly better than the conventional doses which have been used commonly here and elsewhere?

DR. BRICKER: I think one must distinguish between the effect on edema and the effect on the underlying renal lesion. With respect to the treatment of edema, steroid therapy in large doses is definitely an improvement and most observers have been able to diurese the majority of their pure nephrotics. With respect to the effect on the underlying disease, the evidence is not quite so clear, although many observers do believe they may be influencing the natural history of the disease with steroids.

DR. REINHARD: I believe there are patients who do not respond to doses of the magnitude that this patient received but who will diurese very satisfactorily when they are given much larger doses. Is that correct?

DR. BRICKER: Yes, that is correct.

DR. REINHARD: One more problem should be mentioned at least briefly: the convulsions. Dr. Levy, this patient had her first episode of clonic movement of the extremities, followed by mental confusion at a time when her blood pressure was 180/100, her non-protein nitrogen only 38 mg. per cent, and there were no striking alterations in the blood chemical values. Under these circumstances can we attribute the convulsions to uremia, electrolyte imbalance or some other possibility?

DR. IRWIN LEVY: It is still possible to attribute them to the incipient renal failure.

DR. REINHARD: Does one see convulsions as an early manifestation of impending uremia?

DR. LEVY: Occasionally.

DR. REINHARD: Do you think impending uremia is the likely explanation here or do you expect to find some organic brain lesion to account for the convulsions and the abnormal electroencephalogram?

DR. LEVY: I do not expect to find any unusual cerebral pathology.

DR. REINHARD: You think this will all be secondary to the renal lesion? Does anybody wish to take issue with this point of view?

Well, I think we had better try to summarize what has been said. I personally would like to suggest as my first diagnosis, the sequence of events that Dr. Bricker has outlined so nicely here of a chronic glomerular nephritis with acute exacerbation of glomerular nephritis leading to the nephrotic syndrome. Another second, very real possibility, and one for which there is a great deal of evidence, is that this patient had chronic renal disease of infectious origin, either pyelonephritis or possibly a tuberculous renal infection. That diagnosis would not account for the nephrotic syndrome which I think was present, and if the underlying renal lesion turns out to be a chronic pyelonephritis or a tuberculous infection of the kidney, I think we then have to postulate that the patient had a second type of renal disease: either disseminated lupus or amyloidosis or possibly bilateral renal vein thrombosis. The latter seems very unlikely because of its rarity and because the kidneys appear to have been normal in size. The patient also had hypertensive cardiovascular disease presumably of renal origin and we may anticipate therefore that the patient had arteriosclerosis and probably nephrosclerosis so that there may be actually a third type of renal disease present.

PATHOLOGIC DISCUSSION

DR. DAVID EDWARDS: At autopsy, pitting edema of all four extremities and the dependent portions of the trunk was demonstrated in this moderately well nourished Negro woman of small stature. On opening the thoracic cavity, a small amount of fluid was found in the serous cavities and there were a few old fibrous adhesions of the pleurae covering the upper lobes of the lungs. Diffuse, mild emphysema, and areas of patchy atelectasis were seen in the posterior portions of the lungs. A small adherent thrombus occluded a small pulmonary artery in the right lower lobe. The heart (285 gm.) was only slightly enlarged and the coronary arteries were but slightly sclerotic. A small bland thrombus was attached to one of the cusps of the aortic valve. Two hundred and fifty milliliters

FIG. 1. Gross photograph of the kidneys after hemisection showing the extensive cyst formation in the cortex.

FIG. 2. Photomicrograph of a renal gomerulus with the most advanced proliferative changes. Capsular adhesions and pericapsular fibrosis may be noticed.

of serous fluid were found in the peritoneal cavity. Both kidneys were enlarged (combined weight over 600 gm.). (Fig. 1.) Multiple cysts of varying sizes and shapes distorted both renal cortices, leaving small patches of solid parenchyma between them. The cysts impinged on the collecting system and had produced distortion and elongation of the calyces. The pelvic mucosa was grey-white and thickened. The contents of the cysts were varied. Some contained either clear fluid, granular debris, altered blood or even frankly purulent exudate. Microscopically, the cysts were lined by flattened cuboidal epithelium which resembled that of the tubules. Some nephrons were filled with polymorphonuclear leukocytes, and in various regions the latter had extended into the surrounding interstitial tissue. Occasionally the appearance of an abscess was suggested, but the presence of lining epithelium around these dense aggregates of neutrophils indicated that they were, in fact, infected cysts. Throughout the tissue which had persisted between cysts there was a diffuse increase in interstitial fibrous tissue, largely at the expense of the tubules which were small and atrophic and were lined by flattened epithelium. In the surviving parenchyma of both cortex and medulla, groups and streaks of chronic inflammatory cells were evident. Many glomeruli exhibited varying degrees of lobular and pericapsular fibrosis and hyalinization with slight proliferative changes in the glomerular tufts and some capsular adhesions. Some glomeruli were entirely normal. None of the glomerular lesions were characteristic of glomerulonephritis. (Fig. 2.) The arteries and, to a lesser degree, the arterioles were thickened by fibrous intimal proliferation. In summary, the kidneys exhibited the changes both grossly and microscopically of polycystic renal disease upon which there was superimposed a common complication: pyelonephritis (both chronic and acute), with proliferative changes in the vessels secondary to the inflammation.

Petechiae and ecchymoses were observed in the stomach, cecum and bladder with additional evidence of acute inflammatory change in the mucosa of the latter. Pancreatic acini were dilated in the manner often associated with uremia. The brain revealed no abnormalities grossly or microscopically. Cultures taken of the heart's blood and of the left kidney, produced a profuse growth of micrococci (Staphylococcus aureus).

Final anatomic diagnoses: Primary: polycystic kidneys, moderate; acute and chronic pyelonephritis, marked; arteriosclerosis of the renal arteries, moderate; edema of the lower and upper extremities; ascites (250 cc.); atelectasis of dependent portions of the lungs; organizing thromboembolus in a branch of the pulmonary artery to the right lower lobe; congestion of the bladder and liver, slight; petechiae and ecchymoses of the stomach, cecum and bladder; dilatation of pancreatic acini, slight, (clinical history of uremia); lipid depletion of the adrenals, slight; fatty metamorphosis of the liver, slight. Accessory: thrombi of the cusps of the aortic valve; pulmonary emphysema, diffuse, slight; fibrous pleural adhesions of left lung and upper lobe of the right lung; leiomyomas of uterus.

DISCUSSION AFTER PATHOLOGY PRESENTATION

DR. HARTROFT: The relatively small size of these polycystic kidneys is the most unusual

feature of this case from both clinical and pathologic aspects. In 80 to 85 per cent of these cases, the kidneys weigh between one and two kilograms at autopsy. But in today's case, function of renal parenchyma between the cysts had undoubtedly been severely impaired by the accompanying pyelonephritic disease, and her death hastened. In the absence of pyelonephritis, the patient might well have survived several years longer thereby permitting an increase in the size of the cysts, so that the kidneys might then have attained the size more usually associated with fatal polycystic disease in the adult. It is remarkable that this woman survived nine pregnancies without clinical manifestations of her polycystic renal disease throughout any of the gestation periods.

DR. REINHARD: Dr. Hartroft, we're still wondering a little about the nephrotic syndrome that this patient apparently had. Do you think there was enough glomerular disease here to account for a little nephrosis superimposed on her cardiac failure?

DR. HARTROFT: Dr. Edwards demonstrated considerable evidence of both tubular and glomerular damage. It is, however, very difficult to estimate from microsections just how such a variety of lesions would affect the general picture of renal function as evaluated clinically.

DR. RECANT: Dr. Bricker commented on the low protein excretion as one of the factors that made the nephrotic syndrome a little questionable. I wonder how much protein was being excreted into renal cysts which were not in communication with the outflow tract?

DR. REINHARD: Well once the cysts were filled up, this would not happen again.

DR. BRICKER: The protein concentration of cyst fluid varies widely. However, in our experience it has never been equal to and is usually less than the plasma levels.

DR. HARTROFT: It should be remembered that in this disease, and indeed in this particular patient, communications frequently develop between some of the cysts and the renal pelves, so that there would be a constant turn-over in protein-content.

DR. SHERRY: Dr. Reinhard, it is my understanding that the nephrotic syndrome has never been described in either polycystic disease or in chronic pyelonephritis. I wonder whether this is really a nephrotic syndrome or whether we were confused by the dilution of proteins associated with the edema of cardiac and renal failure?

Acknowledgment: Illustrations were made by the Department of Pathology, Washington University School of Medicine.

Case Reports

Polycyclic Nephrotic Syndrome*

DAVID A. RYTAND, M.D. *and* ALVIN J. COX, JR., M.D.
San Francisco, California

THE nephrotic phase of chronic glomerulonephritis rarely if ever occurs more than once,[1,2] and it is widely held that glomerulonephritis itself never recurs once complete healing has been demonstrated by rigorous examinations of the urine and its sediment.[3] In sharp contrast, certain patients have been observed in whom multiple recurrences of the nephrotic syndrome are prominent. Between relapses not only does edema disappear but proteinuria vanishes as well; in addition, a normal serum content of proteins and lipids is sometimes demonstrable in remissions. In view of this contrast it seems appropriate to report in detail on such a patient, who was previously described more briefly by Addis,[4-7] to include results of the subsequent necropsy and to review other cases and relevant literature.

CASE REPORT †

An American cabinet maker (O. R. B., 257032) was fifty-two years old when seen in June, 1937, for the first of eight separate periods of edema. Many attacks of urticaria had occurred between the ages of nine to twenty years and were associated with swelling of face and fingers. This patient had had frequent episodes of poison ivy and on one occasion poison oak dermatitis, but neither occurred after 1931. He was jaundiced at the age of thirteen. A cough, later chronic and productive of a "cupful" of sputum daily, started in 1927. When the patient was seen in 1930 with this complaint, the urine was negative. There was a long story of head colds and sneezing on exposure to sawdust. Stuffiness of the head on awakening which had occurred for two or three months in the spring of 1937 became worse in June, 1937.

During administration of cold vaccine in June, 1937, the patient noted swollen eyelids and face in the mornings. The urine was grossly normal but contained protein. Table 1 presents the pertinent data. A diet was prescribed and by November the edema had disappeared. Microscopic hematuria (5 to 120 million erythrocytes per twenty-four hours) was consistently found as late as May, 1939. One solitary blood cast was seen by Dr. Addis in 1937 and another by one of us (D. A. R.) in 1940. Oval fat bodies and fat droplets in hyaline casts were regularly found during relapses.

The second attack of edema began in December, 1937, after two weeks of a "very bad head cold" and ended nine weeks later. There was no apparent cause for the third attack of edema, which lasted from early April to late May, 1938. The urine was entirely normal for the first time October 3, 1939. The fourth attack occupied May, 1940, occurring one week after "flu." Urinalyses and other relevant examinations were again entirely normal in January and June, 1942.

The fifth episode of edema began in June, 1943, and differed from the earlier attacks in its long duration (six months) and absence of hematuria; erythrocytes in abnormal numbers did not occur again until October, 1946. During the fifth attack electrophoresis revealed that "at a pH of 7.7 the fraction that had the mobility of serum albumin was split in two" both in serum and in urine.[4,7] No significant cause of the episode was recognized.

In March, 1944, the patient noted dermatitis but urinary and all other findings were negative in February and April. The urinary sediment was still normal and no edema was noted June 3, 1944, but the rate of proteinuria was 2.9 gm. per 24 hours; this followed the occurrence of a carbuncle and series of boils. Three days later edema occurred for the sixth time as the serum proteins fell from 6.2 to 5.0 gm. per 100 ml.; proteinuria increased to 11.3 gm. per twenty-four hours as fat-studded hyaline casts and epithelial cells, but not erythrocytes, appeared. In September on the second day of a trip to the mountains edema disappeared. Definite but slight urinary abnormalities persisted and there was an abortive seventh attack of edema in January, 1945. On July 21, 1945, all findings were again normal.

The eighth and final episode began in Ohio on May 1, 1946, during a siege of "sinusitis" or hay fever.

† Many of the observations were made by Dr. Thomas Addis.

* From the Departments of Medicine and Pathology, Stanford University School of Medicine, San Francisco 15, California.

TABLE 1

OBSERVATIONS IN PATIENT O. R. B. (257032)

Date	Edema	Rates of Urinary Excretion (per 24 hr.)				Serum (per 100 ml.)				Arterial Pressure (mm. Hg)	
		Protein (gm.)	Casts (millions)	Erythrocytes (millions)	Leukocytes and Epithelial Cells (millions)	Total Protein (gm.)	Albumin (gm.)	Cholesterol (mg.)	Urea (mg.)	Systolic	Diastolic
June 26, 1937	++	3.17	0.60	20	16	....	....	....	72	140	100
November 2, 1937	0	0.02	0.23	14	1	....	....	....	33	120	90
January 6, 1938	++	4.50	1.50	120	16	....	....	....	82	135	100
March 17, 1938	0	0.20	0	20	4	....	....	....	31	120	90
April 12, 1938	++	0.90	2.20	16	36	3.86	....	217	32	130	90
October 3, 1939	0	0	0	0	0	5.90	....	....	29	105	80
May 16, 1940	++	3.22	0.03	28	4	4.70	....	....	48	155	105
June 2, 1942	0	0.05	0	0	1	7.56	....	....	35	115	85
September 25, 1943	+++	5.10	0.07	3	3	3.75	....	....	32	145	90
February 5, 1944	0	0.03	0	0	0	6.60	....	....	..	120	80
April 29, 1944	0	0.01	0	1	3	6.15	....	....	..	135	95
June 30, 1944	++	8.60	2.40	0	29	3.70	....	....	48	135	95
November 18, 1944	0	0.66	0	0	0	5.00	....	....	29	120	90
January 27, 1945	+	1.41	0	0	5	4.60	....	....	25	130	100
July 21, 1945	0	0.03	0	0	0	....	....	....	33	140	95
September 17, 1946	++++	11.35	4.20	0	40	3.82	2.6	588	31	150	100
May 16, 1947	++++	9.45	0.18	20	32	3.60	1.8	847	93	190	120
October 15, 1947	++++	8.05	1.40	32	19	4.95	2.5	830	95	220	120
August 4, 1948	++++	17.20	+	8	26	4.80	2.6	600	83	170	110

The patient was hospitalized late in October, 1946. Edema extended up to the thoracic wall. The neck veins were flat, the heart was normal. In his deep chest the lungs were "full of sounds which resemble those heard in bronchial asthma." The blood regularly showed eosinophilia of 12 to 16 per cent from this time through June, 1947. The serum titer of antistreptolysin O was 12 units per ml. An x-ray showed a tortuous aorta, congested lungs and a little fluid at the bases. Allergic skin tests were negative except for a strong reaction to a 1:1000 dilution of grass mixture. Epinephrine temporarily abolished wheezes, and diphenhydramine seemed to decrease the cough and rhinitis. Two infusions of plasma failed to induce diuresis, and the patient was dismissed on his usual diet with restricted protein and sodium salts.

The next hospital visit was from May 15 to June 20, 1947. Anasarca was so severe that for three months edema fluid had been escaping by rectum. Advancing retinal vascular changes were noted. The heart was normal. Wheezes in the lung fields were heard. Blood counts revealed anemia and eosinophilia. The venous pressure was 9 cm., circulation time sixteen seconds and vital capacity 2.8 L. The patient received three blood transfusions and twenty-three infusions of salt-poor human serum albumin totalling 1,125 gm.; anasarca disappeared simultaneously with loss of 22 kg., dyspnea was relieved (although wheezes persisted), and the patient felt better in general. Arterial pressure was elevated and relatively constant, serum albumin rose to 3.0 and globulin to 2.2. gm. per 100 ml., urea fell to 36 and cholesterol to 400 mg. per 100 ml. Proteinuria rose to a peak of 66 gm. per day and was usually over 35 to 40, but the numbers of formed elements did not increase.

Edema gradually reappeared and the patient returned to the hospital on October 15, 1947, with dyspnea and orthopnea. Retinal hemorrhages were present for the first time. The neck veins were distended and wheezes were heard as before. After an abdominal paracentesis and transfusions of red blood cell mass on four consecutive days, he received fourteen infusions of serum albumin in as many days (total 675 gm.); results were similar to those obtained earlier and wheezes persisted. An electrocardiogram was normal.

The patient returned again to the hospital August 2, 1948, with anasarca. The neck veins were greatly distended, the heart was questionably enlarged and its sounds were faint. Other findings were similar to those noted previously except for the appearance of renal failure casts. The cephalin flocculation reaction was negative. An electrocardiogram showed low voltage QRS complexes and T waves. Abdominal paracenteses were used to control anasarca. Dyspnea increased and sharply curtailed the patient's activity; pruritus appeared. Relatively minor activity precipitated severe dyspnea and upper abdominal pain one day prior to the final hospital entry on November 18, 1948. Anasarca, orthopnea and great respiratory distress were present. The neck veins were distended and in the lungs wheezes and basal rales were heard. The heart size and sounds were obscure, the rate was 100 and a gallop was present. The arterial pressure was 118/82 mm. Hg. The liver was enlarged and tender, as was the abdomen. Vascular collapse was

present. The patient received the usual supportive measures but, after great restlessness, died on November 19, 1948.

Autopsy revealed that death was the result of infarction of the small bowel caused by thrombosis of the celiac and superior mesenteric arteries, which in turn complicated recent myocardial infarction secondary to coronary thrombosis. Old coronary thrombosis with a myocardial scar was also present and generalized systemic and pulmonary atherosclerosis was observed. There was considerable hyaline thickening of the splenic central arterioles. Both lungs showed diffuse, moderate emphysema; practically all the thin-walled bronchi contained much tenacious gray mucus; most of the alveoli from dependent portions of the lungs contained numerous heart failure cells. Grossly, the liver appeared normal; microscopic sections showed a slight excess of portal connective tissue heavily infiltrated by lymphocytes, and more than the usual variation in size of the hepatic cells, the larger of which often contained two nuclei. The adrenals contained unusually prominent cortical lipoid but were otherwise not remarkable.

The kidneys each weighed 170 gm. and were of normal size. Their capsules stripped easily, revealing outer surfaces which were slightly irregular because of numerous rounded, pale, yellowish nodules approximately 2 mm. in diameter. There was no pronounced scarring, the cortex appeared slightly thin, and the medulla and pelvic and ureteral tissues were normal. Microscopically, the cortex had a varied appearance. Scattered glomeruli were completely fibrosed but most were relatively intact. Among the latter there were occasional glomeruli with tufts adherent to the capsule or with loops adherent to each other. (Fig. 1.) Most glomeruli showed irregular thickening of capillary walls and various degrees of hyalinization; usually this was relatively mild and a few glomeruli appeared normal. Occasionally there was localized pericapsular fibrosis. A number of small, rounded, hyaline structures appeared to lie within the lumens of glomerular capillaries. Many tubules were atrophied, sometimes to a degree which made them inconspicuous in the fibrous tissue of the stroma, which in places contained frequent lymphocytes. In other areas the tubules were of normal size; their epithelium sometimes contained hyaline droplets. Hyaline casts were seen frequently. The large- and medium-sized vessels showed some intimal thickening but little splitting or reduplication of elastic laminas. Some arterioles were distinctly thickened, particularly in the atrophic zones, but this was not severe and many arterioles appeared normal.

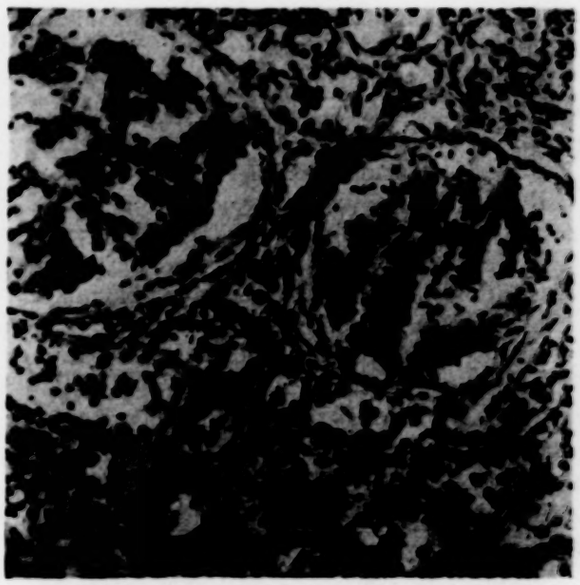


FIG. 1. Photomicrograph of renal tissue from patient O. R. B. Note glomerular adhesions, irregular thickening of tufts and tubular atrophy.

COMMENTS

In this patient the urine was entirely normal as determined by the careful technic of Addis on no fewer than four widely separated occasions between at least six and probably eight relapses of the nephrotic syndrome. Two episodes started in December and January, the remainder in April to June (Heymann and Startzman[8] noted a similar seasonal incidence in children with lipemic nephrosis). Allergic phenomena were prominent both in the past and in the illness under consideration; the onset occurred during administration of a vaccine and four relapses were related temporally to infections or hay fever. Erythrocytes and two blood casts were seen in the urinary sediment at first when mild arterial hypertension and retention of urea occurred. Hematuria was absent thereafter, in both remissions and relapses, until hypertension became persistent toward the end.

Addis regarded this patient[4] and similar ones with polycyclic nephrotic syndrome as instances of "prerenal proteinuria," due not to a primary renal lesion but rather to defective plasma protein formation with renal degeneration consequent to tubular resorption of protein.[4–7,9] Table 26 of his book[9] contains at least three instances of patients with recurrent syndromes, B. H., P. L. and T. C., and possibly a fourth, M. F., whose more detailed history appeared earlier[10] as Case XLIX. It is of some interest that the same Table 26 also includes patient O. E., who had hives as a youth, hay fever, a bullous dermatitis and eczema, and patient D. R., in whom proteinuria followed antiluetic therapy; these patients had been reported earlier (Cases XLVIII and L,

respectively) as instances of cryptic degenerative Bright's disease.[10]

Addis also made most of the following observations in another case of polycyclic nephrotic syndrome. Patient A. J. (A50739) suffered from ichthyosis, eczema and urticaria since early childhood. At the age of two he was edematous for a year. In 1938 (aged fourteen) he was edematous for four months; proteinuria which was then present disappeared later. Edema and proteinuria returned in November, 1941, for the third time but had disappeared by March, 1942, when all relevant examinations in this clinic were negative. Edema and proteinuria reappeared for the fourth time in January, 1946, and continued for more than a year before the former disappeared; proteinuria persisted thereafter. The arterial pressure was 146/116 mm. Hg in 1941, 110/64 mm. Hg in 1942, 210/130 mm. Hg in 1946 in relapse, remission and relapse, respectively. The urine contained 8 and 80 million erythrocytes per twenty-four hours in 1941 and 1946, respectively, in which years the concentrations of cholesterol in the serum were 458 and 467 mg. per 100 ml. The patient died with uremia and arterial hypertension in 1952.

Addis observed another patient in whom relapsing proteinuria appeared after a bee sting, and in still another patient in this clinic a few entirely normal specimens of adequately examined urine were noted during the course of lipemic nephrosis which accompanied and followed "antigen sickness" initiated by a bee sting.[11]

Barnett et al.[12] described a patient with polycyclic nephrotic syndrome in whom each of three episodes was precipitated by the use of trimethadione; moderate degrees of arterial hypertension, microscopic hematuria and retention of urea occurred in relapses. Derow[13] reported on the course of a thoroughly studied patient in whom there were also three episodes of polycyclic nephrotic syndrome separated by intervals in which pertinent abnormalities disappeared. One relapse occurred three weeks after the use of penicillin for a boil on the wrist, other suppurative episodes were not followed by recurrence. Hypertension, hematuria and retention of nitrogen were virtually absent in relapses. Dr. Derow gave the following additional information in a letter of March 25, 1955: the patient suffered another series of boils early in 1949 without relapse; his arterial pressure and the results of careful urinalyses were normal both in Dr. Derow's hands later in 1949 and 1950 and in an examination elsewhere; he was accepted for life insurance in September, 1954; a dermatitis (eczema, atopic dermatitis or neurodermatitis) continued, but he was well otherwise except for hay fever. It is noteworthy that postural proteinuria was present temporarily during the second remission. Others[8] report an increased incidence of postural proteinuria after apparent healing in nephrotic subjects and note this as a possible source of error in evaluating relapse or remission. This error was avoided by Derow.[13] Another obvious pitfall, failure to find urinary abnormalities during apparent remission because of inadequate urinalyses, probably was not a source of error in any of the cases reported or cited herein.

Camelin et al.[14] obtained a necropsy of one of their patients, a thirty-two year old man, in whom there were also two cycles. All the features of lipemic nephrosis were present in 1942 to 1944; in March, 1946, proteinuria was absent and the concentrations of albumin, globulin and cholesterol in the serum had become normal, but relapse with uremia and hypertension occurred in October, 1946. The necropsy[15] showed hyalinized, sclerotic, fatty glomeruli and fat in the tubules and elsewhere. Ehrich[16] reported somewhat similar findings in a remarkable patient in whom the nephrotic syndrome persisted for seventeen years; although this was probably not a truly polycyclic syndrome, the clinical report mentions two negative urinalyses of urine specimens with high specific gravities.[17]

Heymann et al., with an extensive experience in children with the nephrotic syndrome, observed only one child with two spontaneous cycles.[18] Major[19] saw a patient with cycles of relapse separated by almost two decades. Contratto[20] noted a relapse precipitated by infectious mononucleosis. In still another case, after a relapse following sixteen years of remission terminated fatally, necropsy revealed polyarteritis and thrombosis of the renal veins without glomerular lesions;[21] at least the polyarteritis may have been the result of a reaction, with urticaria and asthma, to penicillin given after the onset of relapse.

The nephrotic syndrome in patients with chronic quartan malaria has returned together with malaria after relatively enduring remissions of both induced by quinine.[22,23] In recent years, of course, relapses have occurred in many nephrotic patients after more or less temporary

and often incomplete remissions induced by cortisone, corticotropin, measles, etc. In all of the patients discussed, however, the remissions were spontaneous.

Because these patients exhibited the triad of hematuria, hypertension and renal failure in varying degrees during relapses one might conclude that in each there were recurrences of repetitively healing glomerulonephritis. This interpretation receives superficial support from the demonstration of lesions of glomerulonephritis in two of the necropsies.

Proliferative glomerulonephritis of the poststreptococcal variety (hemorrhagic Bright's disease) is not known to relapse after verified healing, nor does its nephrotic phase occur more than once.[1–3] On clinical grounds, therefore, this type of nephritis seems an unlikely background for polycyclic nephrotic syndrome in the latter's entirety. However this or a similar lesion might have contributed to the terminal relapse in some of the patients including O. R. B.; furthermore, the blood casts found early in the course of patient O. R. B. were probably associated with glomerulitis. Note should be taken that studies by means of renal biopsy have demonstrated that glomeruli may become almost completely hyalinized within five weeks.[24]

In addition to the rather unlikely possibility that these patients represent instances of recurrent nephritis complicated regularly by a "nephrotische Einschlag," there is also the possibility that their polycyclic nephrotic syndromes are fundamentally "pure lipemic nephrosis" complicated by varying degrees of proliferative glomerulitis. The essential change in the nephrotic syndrome appears to be the excessive passage of plasma proteins through the glomerular basement membrane, which may become thickened with the lesions of so-called membranous glomerulonephritis.[25] In both human material and in rats with the nephrotic syndrome evoked by immunologic methods, proliferative and exudative glomerular lesions have been found in addition to thickening of the basement membrane.[26] The pathogenesis of these lesions is not necessarily that of the lesions with hemorrhagic Bright's disease, although at times these are histologically rather similar.

This interpretation appears the more attractive, especially as spontaneous remissions occur during the course of experimental nephrotic syndrome of rats.[18,27,28] Dr. Heymann has kindly written that during such remissions, which might last for several months before proteinuria recurred, ascites and edema were absent and proteinuria was not found although urinalyses were done at least weekly; hypertension may or may not have been present, and it was assumed that hyperlipemia was absent ordinarily although slightly increased fat values may have been present in some rats during remission.[28]

Histologic lesions including focal glomerular scarring and adhesions were observed in rats that were believed to be cured[27,28] and therefore may have been present during remissions as well. Furthermore, the technic of renal biopsy in man has produced evidence of thickening of the glomerular basement membrane and other anatomic abnormalities at times when there is no proteinuria at all in some patients or when this is minimal in others.[29,30] It seems possible that polycyclic nephrotic syndrome may be associated with a continuing rather than a recurrent membranous glomerulonephritis, but additional observations are required to determine this.

SUMMARY

A detailed report is presented of a patient in whom there were at least six and possibly eight separate episodes of the nephrotic syndrome without proteinuria in remissions.

Other examples of polycyclic nephrotic syndrome with two to four cycles of relapse are reviewed. In some not only the urine but also the blood proteins and lipids were normal in remissions. Microscopic hematuria, arterial hypertension and renal insufficiency were present in varying degrees during relapses. There was a high incidence of allergic manifestations in this group of patients.

The patient described herein became uremic and hypertensive. Necropsy showed membranous glomerulonephritis with glomerular adhesions and fibrosis. Similar clinical courses occurred in at least two other patients, with comparable findings in one necropsy.

Polycyclic nephrotic syndrome is probably not an exception to the observation that proliferative glomerulonephritis of the hemorrhagic Bright's disease type does not recur once it has healed. Rather it appears to be a variant of lipemic nephrosis clinically and may be associated with membranous glomerulonephritis. It is suggested that the glomerular lesion may persist during clinical remissions.

REFERENCES

1. Bloom, W. L. and Seegal, D. The nephrotic phase: its frequency of occurrence and its differential diagnostic value in determining the nature of the renal lesion in 120 patients who died of renal failure. *Ann. Int. Med.*, 25: 15, 1946.
2. Addis, T. Haemorrhagic Bright's disease. I. Natural history. *Bull. Johns Hopkins Hosp.*, 49: 203, 1931.
3. Seegal, D. and Earle, D. P., Jr. A consideration of certain biological differences between glomerulonephritis and rheumatic fever. *Am. J. M. Sc.*, 201: 528, 1941.
4. Addis, T. Renal degenerations due to protein reabsorption by the kidney. *Stanford M. Bull.*, 3: 67, 1945.
5. Addis, T., Barrett, E., Poo, L. G. and Ureen, H. Prerenal proteinuria. I. Particle size. *Arch. Int. Med.*, 88: 337, 1951.
6. Persike, E. C. Prerenal proteinuria. II. Observations on the urinary protein. *Arch. Int. Med.*, 88: 346, 1951.
7. Jameson, E. and Addis, T. Prerenal proteinuria. III. Electrophoretic studies. *Arch. Int. Med.*, 88: 350, 1951.
8. Heymann, W. and Startzman, V. Lipemic nephrosis. *J. Pediat.*, 28: 117, 1946.
9. Addis, T. Glomerular Nephritis. Diagnosis and Treatment. New York, 1948. Macmillan Co.
10. Addis, T. and Oliver, J. The Renal Lesion in Bright's Disease. New York, 1931. Paul B. Hoeber, Inc.
11. Rytand, D. A. Onset of the nephrotic syndrome during a reaction to bee sting. *Stanford M. Bull.*, 13: 224, 1955.
12. Barnett, H. L., Simons, D. J. and Wells, R. E., Jr. Nephrotic syndrome occurring during tridione therapy. *Am. J. Med.*, 4: 760, 1948.
13. Derow, H. A. Repeated nephrotic episodes with normal urine, serum protein and cholesterol in the edema-free intervals. *New England J. Med.*, 240: 131, 1949.
14. Camelin, A., Garnung, H. and Forestier. Action favorable immédiate des injections de plasma sur l'anasarque et les troubles humoraux d'une néphrose lipoïdique. *Lyon méd.*, 177: 283, 1947.
15. Coumel, H., Camelin, A., Feroldi, J. and Accoyer, P. Constatations anatomo-pathologiques au sujet d'une néphrose lipoïdique, suivie pendant sept anées. *Presse méd.*, 59: 829, 1951.
16. Ehrich, E. Lipoid nephrosis of unusual duration. II. Pathologic-anatomic report. *Arch. Int. Med.*, 45: 749, 1930.
17. MacKay, E. M. and Johnston, C. Lipoid nephrosis: report of a case of unusual duration. *Arch. Int. Med.*, 45: 734, 1930.
18. Heymann, W., Gilkey, C., Salehar, M. and Gold, E. Influence of sodium salicylate and sodium gentisate on proteinuria of lipemic nephrosis. *J. Lab. & Clin. Med.*, 35: 737, 1950.
19. Major, R. H. Chronic lipoid nephrosis in retrospect. *Am. Practitioner*, 1: 683, 1950.
20. Contratto, A. W. Infectious mononucleosis. *Arch. Int. Med.*, 73: 449, 1944.
21. Miller, G., Hoyt, J. C. and Pollock, B. E. Bilateral renal vein thrombosis and the nephrotic syndrome. Associated with lesions of polyarteritis nodosa. *Am. J. Med.*, 17: 856, 1954.
22. Giglioli, G. Clinical notes, autopsy and histopathological findings from five fatal cases of quartan malarial nephritis from British Guiana. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 26: 177, 1932.
23. Surbek, K. E. A striking case of quartana-nephrosis. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 25: 201, 1931.
24. Brun, C., Hilden, T., Iversen, P. and Raaschou, F. Diseases of the kidney. *Ann. Rev. Med.*, 7: 245, 1956.
25. Allen, A. C. The clinicopathologic meaning of the nephrotic syndrome. *Am. J. Med.*, 18: 277, 1955.
26. Ehrich, W. E., Forman, C. W. and Seifter, J. Diffuse glomerular nephritis and lipid nephrosis. Correlation of clinical, morphological, and experimental observations. *Arch. Path.*, 54: 463, 1952.
27. Heymann, W. and Lund, H. Z. Nephrotic syndrome in rats. *Pediatrics*, 7: 691, 1951.
28. Heymann, W. Personal communications.
29. Brun, C., Gormsen, H., Hilden, T., Iversen, P. and Raaschou, F. Diabetic nephropathy. Kidney biopsy and renal function tests. *Am. J. Med.*, 15: 187, 1953.
30. Iversen, P., Bjørneboe, M. and Krarup, N. B. Biopsy studies of the liver and kidney. *Advances Int. Med.*, 6: 161, 1954.

Hypertension Due to Segmental Infarction of the Kidney*

J. Alex Haller, Jr., M.D., Leo R. Radigan, M.D. *and* Andrew G. Morrow, M.D.
Bethesda, Maryland

Unilateral renal disease as the causative factor in severe hypertension is a well established clinical entity. In remarkably few instances, however, has the time relationship between the kidney disease and the onset of hypertension been well documented. In the cases reported by Howard and associates[1] in one patient hypertension developed seventeen days after a possible renal embolus. With non-operative treatment this patient's blood pressure gradually returned to normal. In Perera's survey[2] there is a single case in which hypertension is known to have developed within a year following renal artery obstruction. This patient's blood pressure returned to normal after nephrectomy. Poutasse[3] has recently reported another case in which hypertension developed within five months following an embolus to the renal artery. This patient's blood pressure also returned to normal following nephrectomy.

We have recently had the opportunity to study a patient in whom the time relationship between renal infarction and subsequent hypertension was exceptionally well documented.

CASE REPORT

A forty-two year old housewife was admitted to the Surgical Service of the National Heart Institute on September 20, 1954 with the diagnosis of mitral stenosis. She complained of progressive shortness of breath and marked fatigability. During the previous four years she had had three arterial emboli, one cerebral and two to the lower extremities. The blood pressure was 120/70. There was slow atrial fibrillation and the characteristic murmur of mitral stenosis. This diagnosis was substantiated by angiocardiography, right heart catheterization and transbronchial left heart catheterization.

At 5 A.M. on October 2, 1954, two days prior to proposed cardiac surgery, the patient was awakened by intense non-radiating pain in the left flank. She was slightly nauseated. Peripheral pulses were unchanged, the abdomen was soft and she was afebrile. A specimen of urine contained no cells or albumin.

A diagnosis of splenic infarction was made and the patient was given dicumarol. Within eighteen hours

Fig. 1. Retrograde renal arteriogram demonstrating occlusion of the segmental artery to the lower pole of the left kidney.

the pain had diminished and in three days disappeared entirely. A specimen of urine collected four days after the onset of pain contained a trace of protein but no cells or casts. A mitral commissurotomy was performed on October 19, 1954, seventeen days after the attack. The postoperative course was benign and the blood pressure remained normal. Whole blood urea nitrogen values of 15 and 17 mg. per 100 cc. were recorded in the postoperative period. The patient was

* From the Clinic of Surgery, National Heart Institute, Bethesda 14, Maryland.

FIG. 2. The left kidney which was removed at operation. The lower pole is small and the segmental artery is occluded by a thrombus.

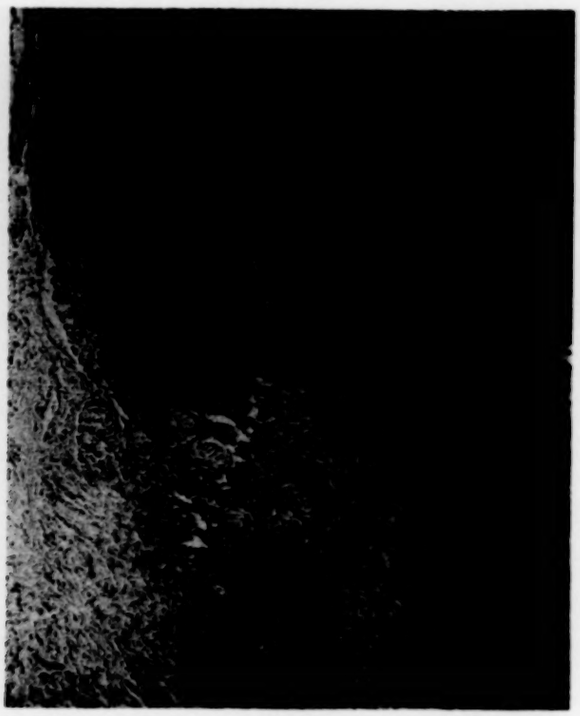


FIG. 3. Section through transition zone of left kidney showing necrotic glomeruli of the infarct partially replaced by infiltrating fibrous tissue. The adjacent viable structures show segmental glomerular hyalinization and moderate endothelial proliferation of the smaller arterioles.

discharged to the care of her referring physician on November 24, 1954.

She experienced a gradual increase in exercise tolerance and had no dyspnea or pain. Frequent determinations of the blood pressure by her physician were normal. She remained well until January 2, 1955. On this day she experienced the first of daily frontal headaches. On January 5, she saw her physician and was found to have a blood pressure of 160/110. There were no retinal changes. It had been ninety-five days since the episode of embolic pain. The headaches increased in severity and frequency and on January 10 her systolic blood pressure was 220 mm. Hg. She was found to have retinal hemorrhages and exudates. Specimens of urine at this time contained no cells or protein.

She was readmitted on January 13, 1955. The blood pressure at this time was 210/116. The pulse was 80. There was marked retinal arterial spasm and numerous globular and flame-shaped hemorrhages. There was striking A-V nicking but no papilledema.

Examination of the urine was again normal. Blood urea nitrogen was 16 mg. per 100 cc. An intravenous pyelogram showed prompt bilateral dye excretion but there was diminished concentration on the left where the calyces were poorly visualized. A urine concentration test revealed a maximum specific gravity of 1.035. An intravenous regitine® test was negative. Hexamethonium (15 mg.) was given intravenously over a fifteen minute period with a dramatic fall in blood pressure to 120/80.

The patient was maintained on subcutaneous hexamethonium, 15 mg. every four hours for forty-eight hours. During this period the systolic blood pressure was maintained below 180 mm. Hg and she remained free of headaches. Retrograde pyelography revealed contraction of the calyceal system on the left, compatible with a small left kidney. Differential volumetric urine samples showed that the volume excreted by the right kidney was ten times that of the left. The two hour phenolsulfonphthalein excretion was 54 per cent.

During the second forty-eight hours of hospitalization it was necessary to increase the hexamethonium dosage to 25 mg. every three hours in order to maintain a systolic pressure below 180 mm. Hg. There was intermittent return of frontal headaches. A retrograde aortagram was performed percutaneously by means of a catheter passed via the femoral artery to the level of the renal vessels. Twenty cc. of 70 per cent urokon® were injected at this site and serial films revealed occlusion of the inferior branch of the left renal artery. (Fig. 1.) A diagnosis of renal infarction secondary to

arterial occlusion seemed established. In the next forty-eight hours adequate blood pressure control became more and more difficult despite increasing doses of hexamethonium.

On January 20, 1955, a left nephrectomy was performed. The lower pole of the excised kidney was replaced by adipose and fibrous tissue in the infarcted area. The renal artery to this pole was occluded by organized thrombus. (Fig. 2.) Microscopically, this portion of the kidney showed almost complete medullary fibrosis. The tissue from the superior portion of the kidney revealed thickening of numerous glomeruli while others were hyalinized or scarred. The microscopic characteristics of acute infarction were observed in the transition zone. (Fig. 3.)

Postoperatively, the blood pressure did not exceed 130 systolic for the first four days, but the blood urea nitrogen rose to 40 mg. per 100 cc. on the fifth postoperative day. At this time the patient again complained of mild headache and the blood pressure was 210/100. The urinary output exceeded 2,000 cc. daily with a specific gravity of 1.008 to 1.010. On the sixth day after operation the blood urea nitrogen was 56 mg. per 100 cc. and the highest blood pressure was 180/95. Thereafter the blood urea nitrogen slowly fell and the blood pressure became stabilized at 140–160/85–90. On the eighteenth day an intravenous pyelogram showed normal function of the right kidney. On the twenty-first day she was discharged. The blood urea nitrogen at this time was 30 mg. per 100 cc. and the blood pressure 140/80.

The patient has been asymptomatic for the past fourteen months and has gained eight pounds. Her blood pressure is 100/60. The urinalysis and blood urea nitrogen are normal.

COMMENTS

The postoperative course of this patient, complicated by transient return of elevated blood pressure, polyuria and azotemia, may in part reflect secondary vascular changes in the remaining kidney. This assumption is based upon the extensive glomerular lesions observed in the viable portion of the excised kidney. These changes were apparently secondary to the hypertensive state. The patient's subsequent recovery emphasizes the reversibility of these lesions.

In his original experimental studies, Goldblatt[4] demonstrated the necessary role of parenchymal ischemia in the production of hypertension. In this patient there was considerable viable tissue adjacent to the infarcted area and this may have represented such an area of renal ischemia.

Perera[2] has emphasized the rapid and "malignant" course of hypertension associated with unilateral renal disease as contrasted with that seen in essential hypertension or bilateral renal disease. Eleven days after hypertension was first detected in this patient, she was seriously ill with constant headache, marked hypertension and retinopathy.

SUMMARY

A case is presented of unilateral renal infarction resulting in hypertension ninety-five days later. The segmental arterial occlusion was demonstrated by retrograde aortography. Following nephrectomy, the patient's blood pressure returned to normal and has remained so for a period of fourteen months.

REFERENCES

1. Howard, J. E., Berthrong, M., Gould, D. M. and Yendt, E. R. Hypertension resulting from unilateral renal vascular disease and its relief by nephrectomy. *Bull. Johns Hopkins Hosp.*, 94: 51, 1954.
2. Perera, G. A. and Haelig, A. W. Clinical characteristics of hypertension associated with unilateral renal disease. *Circulation*, 6: 549, 1952.
3. Poutasse, E. F. Occlusion of a renal artery as a cause of hypertension. *Circulation*, 13: 31, 1956.
4. Goldblatt, H. The Renal Origin of Hypertension. In American Lectures in Pathology, American Lecture Series Publication 14, Cannon, P. R., ed. Springfield, Ill., 1948. Charles C Thomas.

Tricuspid Stenosis*

Report of a Case, with Hemodynamic Studies at Tricuspid Commissurotomy

ALVIN J. GORDON, M.D., GABRIEL GENKINS, M.D.,† ARTHUR GRISHMAN, M.D. *and* ROBERT A. NABATOFF, M.D.

New York, New York

TRICUSPID stenosis of sufficient severity to require surgery is relatively rare. It is even more unusual to observe a patient in whom this lesion is not complicated by hemodynamically significant mitral stenosis or disease of other valves. We recently studied such a case and obtained simultaneous pressure pulse tracings on the operating table, before and after valvulotomy. This afforded us an opportunity to observe the clinical and hemodynamic effects of tricuspid stenosis in a heart that was unaffected by other valvular lesions.

HISTORIC

Hemodynamic studies in a case of "almost pure" tricuspid stenosis, proved by surgery, were first published by Gorlin and Gorlin [*1*]. Ferrer et al. [*2*] discussed the physiologic implications in one patient (with sinus rhythm) who was operated upon for mitral commissurotomy and who died the day after surgery. In this case, tricuspid stenosis of considerable degree was also present. These authors reconstructed the pressure curves from the right atrium and ventricle, redrawing them as if they had been recorded simultaneously, to emphasize the pressure gradient during diastole. Considerable stress was placed on the pressure difference between the two chambers at the Z point, just prior to the onset of ventricular contraction.

Individual instances of tricuspid valvulotomy have continued to appear in the medical literature [*3–6*]. McCord, Swan and Blount [*7*] reported three patients, in one of whom simultaneous pressure pulses were obtained in the right atrium and right ventricle during cardiac catheterization, by means of a double-lumen catheter.

The diagnosis of tricuspid stenosis was recently discussed in some detail by Gibson and Wood [*8*]. Their article includes physiologic data in fifteen cases, and presents pressure tracings in the right atrium and ventricle which were taken on the operating table before and after valvulotomy in one patient. In only one case, a patient with disseminated lupus erythematosus, was the tricuspid lesion thought to be an isolated one.

CASE REPORT

This was the first Mount Sinai Hospital admission for this thirty-two-year old white woman. At the age of six, following a succession of severe sore throats, tonsillectomy was performed. At that time a cardiac murmur was described, although no preceding episode of rheumatic fever was known. At the age of sixteen the patient had an appendectomy for a severe episode of abdominal pain. In the immediate postoperative period and for one year thereafter she suffered from multiple arthralgias and arthritis principally affecting the wrists, elbows and knees. A diagnosis of rheumatic fever was made and salicylates were given. At the age of eighteen the patient noted dyspnea, fatigue and palpitation on exertion. Orthopnea, paroxysmal nocturnal dyspnea, peripheral edema or any other manifestation of congestive heart failure never developed. There was no cough or hemoptysis. In 1953 the patient was hospitalized for five days in another institution because of a persistent bout of palpitation. This responded readily to medical management.

During the year prior to the present admission two symptoms became prominent. There was increasing fatigue on the mildest exertion, more severe than

* From the Departments of Medicine and Surgery, The Mount Sinai Hospital, New York. This investigation was supported in part by a research grant (H-2168) from the National Heart Institute of the National Institutes of Health, Public Health Service.

† Postdoctorate Trainee, National Heart Institute, United States Public Health Service (H-437).

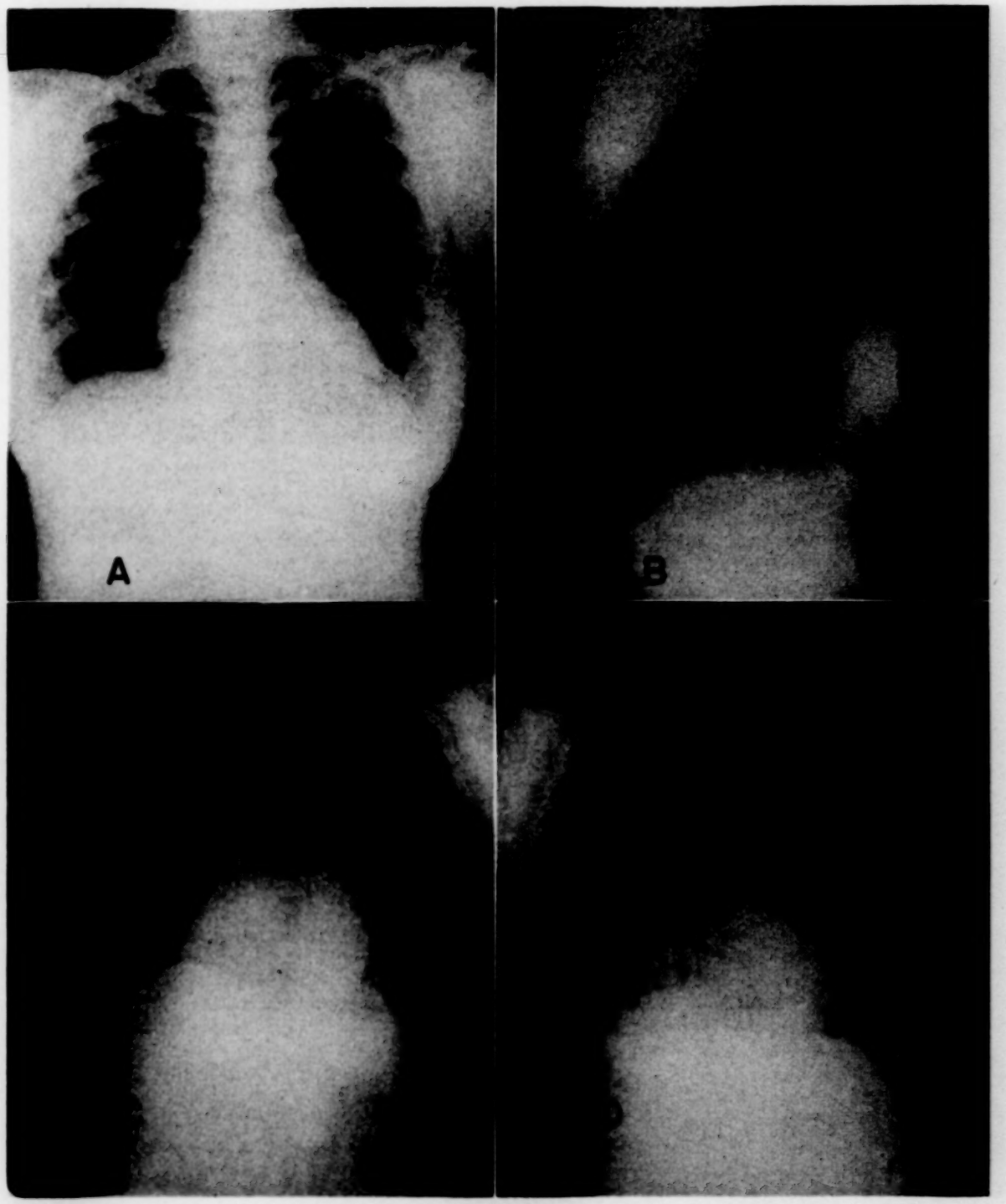


FIG. 1. A, B, C and D. X-rays in posteroanterior, right lateral, left anterior oblique and right anterior oblique projections. Note slight transverse enlargement in (A) with normal pulmonary vascular markings; absence of left atrial enlargement in (B and D) and shelf-like projection of large right atrium in (C).

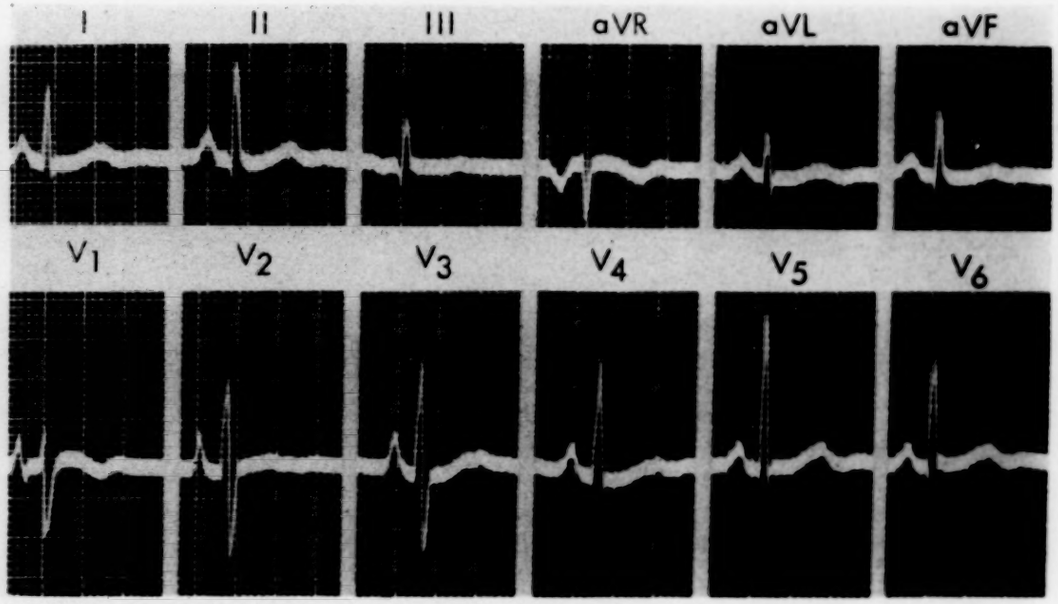


FIG. 2. In electrocardiogram, note prominent P waves in leads V_1, V_2 and V_3, suggesting right atrial enlargement.

previously noted. Secondly, the patient described attacks of sharp pain localized in the right upper quadrant of the abdomen, provoked by exercise. These had previously occurred once or twice a year but now became an almost daily occurrence, forcing marked restriction of activity. The pain responded to sedation and analgesics, and on several occasions improved after intramuscular injection of a mercurial diuretic. For these symptoms the patient presented herself to Dr. Charles Brim who referred her to one of us (R. N.) for surgical treatment.

On physical examination she was a well developed, well nourished young white woman in no acute distress. The blood pressure was 120/70 and the pulse rate 84. All the significant findings were related to the cardiovascular system. There was no peripheral cyanosis, clubbing or edema. Peripheral arterial pulses were normal. Very prominent pulsations were noted in the neck and right upper quadrant. A hepatojugular reflux was present. The jugular venous pulsations were synchronous with the hepatic pulsations rather than with the carotid pulse. Clinically they were judged to be presystolic in time. The chest was normal in configuration. The lungs were clear to percussion and auscultation. Inspection and palpation revealed a point of maximum impulse in the sixth left intercostal space just lateral to the midclavicular line. Medial to the apex a short, harsh early systolic murmur, grade 2 to 3 in intensity, followed a mildly accentuated first sound. A holodiastolic rumbling murmur with presystolic accentuation was heard in the same area. These same murmurs were somewhat louder to the right of the xiphoid cartilage. At the base, the second pulmonic sound was not accentuated and was less prominent than the second aortic sound. A short, faint mid-diastolic blowing murmur was heard at times to the left of the sternum in the third intercostal space. No thrill was palpable nor could a valvular opening snap be heard with certainty at any location.

There was no clinical evidence of ascites. The liver was only minimally enlarged but very forceful pulsations, identical in timing with the jugular pulsations, were clearly appreciable. Manual pressure over the right upper quadrant elicited pain identical with that spontaneously experienced by the patient upon exertion.

The blood count and urine analysis revealed values within normal limits. The red cell sedimentation rate was normal.

Radiographic and fluoroscopic examination (Fig. 1) showed no abnormalities of the lung and diaphragms. Neither a double contour nor increased prominence of the middle segment of the left cardiac contour was noted. The heart was enlarged to the right with a rounding of its right contour. In the left anterior oblique projection the right atrial segment was seen to protrude anteriorly with an increased anterior convexity. The barium-filled esophagus was very slightly indented and displaced posteriorly. On fluoroscopic examination the right atrium and superior vena cava showed vigorous presystolic pulsations. A small linear calcification was seen at the junction of the inferior vena cava and the cardiac silhouette; this was thought to be in the pericardium.

The electrocardiogram (Fig. 2) showed regular sinus rhythm with markedly prominent P waves in leads V1, V2 and V3. In V1 the P wave was diphasic

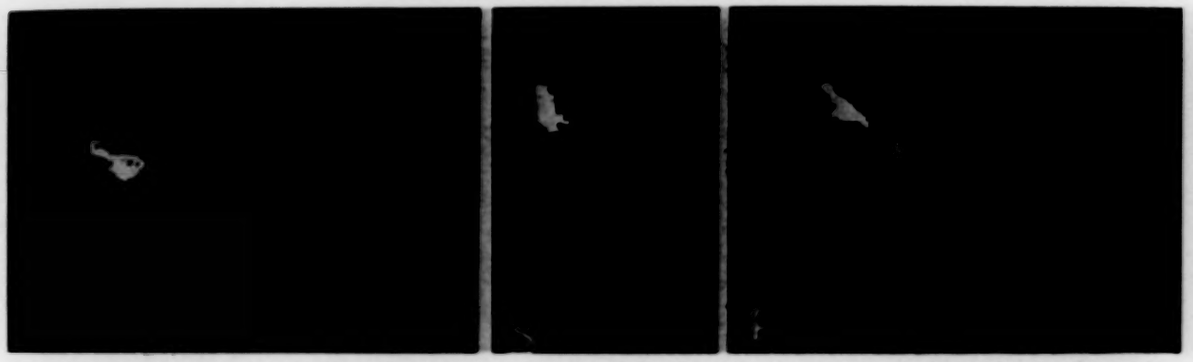


FIG. 3. Vectorcardiogram—horizontal, sagittal and frontal projections. There is a normal QRS sE loop. The P loop, which is inscribed within the larger QRS loop, is unusually prominent and is directed anteriorly, suggesting right atrial enlargement.

and in V2 and V3 the P-R interval was depressed. These findings were regarded as suggestive of right atrial preponderance. The vectorcardiogram (Fig. 3) showed the atrial vector to be anteriorly oriented, which was most suggestive of right atrial preponderance. Neck vein and liver pulse tracings showed very prominent A waves. Phonocardiograms revealed a prolonged diastolic murmur with presystolic accentuation to the right of the sternum at the fourth and fifth intercostal spaces. A similar murmur was recorded over the apex. Accessory sounds such as the opening snap of the mitral or tricuspid valves were not noted, nor was the second sound reduplicated.

Upon cardiac catheterization the catheter entered and coiled in a very large right atrium. Repeated attempts to enter the right ventricle with catheters of different sizes failed. Pressure pulses taken within the right atrium revealed giant A waves. (Fig. 4.)

Although the diagnosis of tricuspid stenosis appeared to be established, mitral stenosis could not be ruled out. Because tricuspid valvulotomy in the presence of mitral stenosis might lead to a serious degree of pulmonary vascular congestion, it was decided to explore the left side of the heart and first perform mitral valve surgery if necessary. The advisability of bilateral commissurotomy at the same operation, by means of an anterior, sternal-splitting approach, was considered but rejected in favor of a two-stage operation.

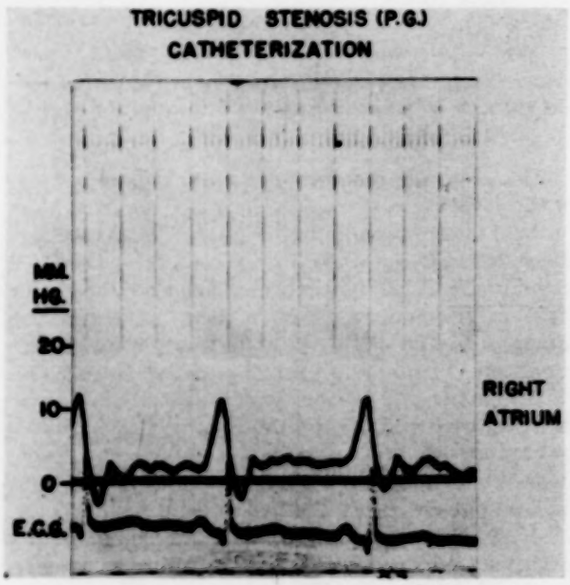


FIG. 4. Right atrial pressure pulse obtained during cardiac catheterization, showing giant A wave. (In this and all subsequent pressure tracings, paper speed was 50 mm./sec., and electrocardiogram was lead 2. Heavy time lines are 0.2 seconds apart.)

First Operation. On December 6, 1955 the left pleural cavity was entered through the fourth intercostal space. The lungs, the left atrium and left ventricle were normal in appearance The left atrial appendage was small. A faint diastolic thrill was palpable over the right side of the heart but not over the left, and direct auscultation with both a stethoscope and a condenser microphone disclosed a diastolic murmur in a corresponding location.

Simultaneous pressure pulses in the left atrium, left ventricle and aorta (Fig. 5) were obtained by needle puncture according to a method previously described [9] in which all three manometers are adjusted to equal sensitivity and the tracings inscribed with identical zero points and equal ordinate scales. As seen on the oscilloscopic screen, there was no appreciable filling pressure gradient between the left atrium and ventricle, indicating the absence of mitral stenosis. The left atrial appendage was so small that it did not permit insertion of the surgeon's index finger and the mitral valve was explored with the fifth finger instead. The edges of the valve were slightly thickened but there was no stenosis or indeed any interference with valve function. A biopsy specimen of the lung was taken, which was subsequently reported as normal.

Second Operation. The patient withstood the first procedure well. The second stage was performed nine days later, through the right fourth intercostal space.

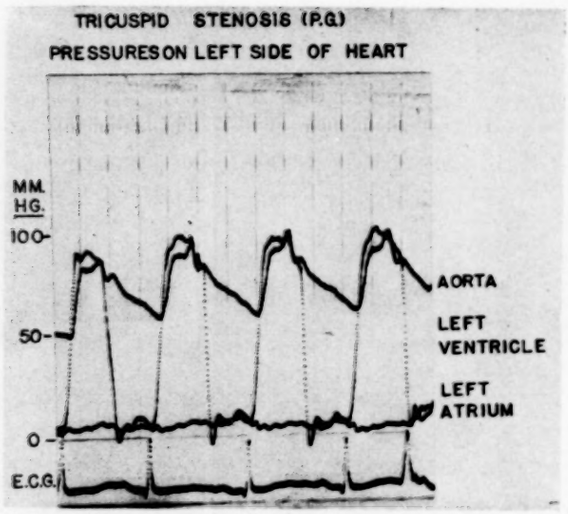


FIG. 5. Simultaneous triple pressures in the left atrium, left ventricle and aorta during the first operation.

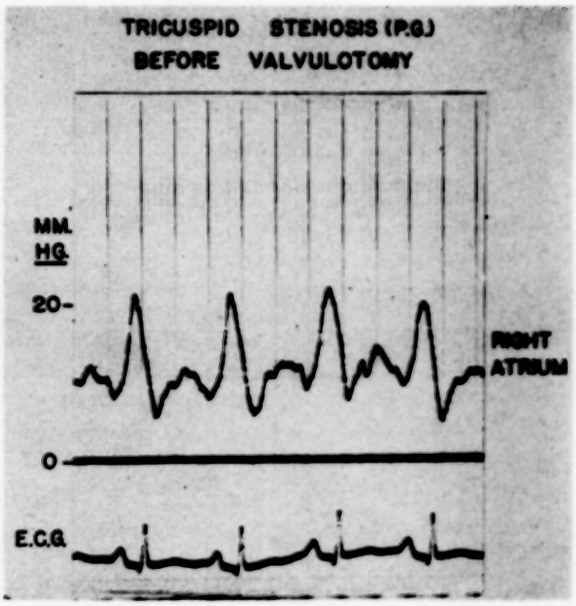


FIG. 6. Pressure pulse obtained in the right atrium during the second operation, before valvulotomy.

Fibrinous pericarditis was present, an expected result of the initial operation. The heart presented a most unusual appearance, in that a huge right atrium was the only structure visible in the wound. It extended down to the diaphragm and medially underneath the sternum. It was tense, bluish in color, and contracted vigorously. The right ventricle could not be immediately identified. The pulmonary artery was finally felt beneath the sternum and the location of the right ventricle just inferior to it was established when a characteristic pressure pulse was obtained by needle puncture. Simultaneous pressure pulses in the right atrium and ventricle exhibited a distinct filling pressure gradient, and established the diagnosis of tricuspid stenosis. (Figs. 6 and 7.) The surgeon, inserting an index finger through the atrial appendage (which was not particularly large) located the tricuspid valve with some difficulty. It was medial, rather than inferior, to the atrium. The valve was funnel-shaped and did not admit a finger tip. No commissures could be identified. After considerable manipulation the valve was widely split, by the finger, in a posterolateral direction so that it was estimated that it would easily admit two fingers. A small regurgitant jet which was palpable at the beginning of the procedure could not be felt at the completion of valvulotomy.

The atrium began to shrink in size almost immediately, lost its turgor, and its contractions were less vigorous. Pressure pulses obtained about fifteen minutes after valvulotomy revealed a marked decrease in the height of the A wave and in the filling pressure gradient between atrium and ventricle. (Figs. 8 and 9.)

Although recovery after both operations was uneventful, it was not until after the second procedure that symptomatic improvement was noted. Despite distress from the bilateral wounds the patient noted absence of the sense of heaviness in the right upper quadrant which, coupled with pain, had been a chief symptom. As soon as she became ambulatory activity was tolerated far better than after the first procedure.

She subsequently became pregnant and delivered without difficulty.

HEMODYNAMIC STUDIES

The right atrial pressure pulse obtained at cardiac catheterization (Fig. 4) revealed a giant A wave, reaching a height of 12 to 14 mm. Hg. A sharp drop in pressure occurred with atrial relaxation, with a relatively rapid rise during early ventricular contraction, and subsequent plateau. The mean right atrial pressure was 8 mm. Hg. Excluding atrial contraction the pressure in the atrium during the greater part of diastole was low, about 4 mm. Hg. In the absence of a ventricular curve for comparison, this fact cast some doubt upon the diagnosis of tricuspid stenosis.

Pressures in the left side of the heart during the first operation (Fig. 5) were probably within normal limits. The left atrial pressure pulse was of normal configuration, and the mean left atrial pressure was 5 mm. Hg, a normal figure. With the exception of the early diastolic dip in the ventricle (possibly an artefact) the atrial and ventricular curves did not diverge during diastole. The anacrotic notch in the aortic pressure pulse is probably an artefact. We have

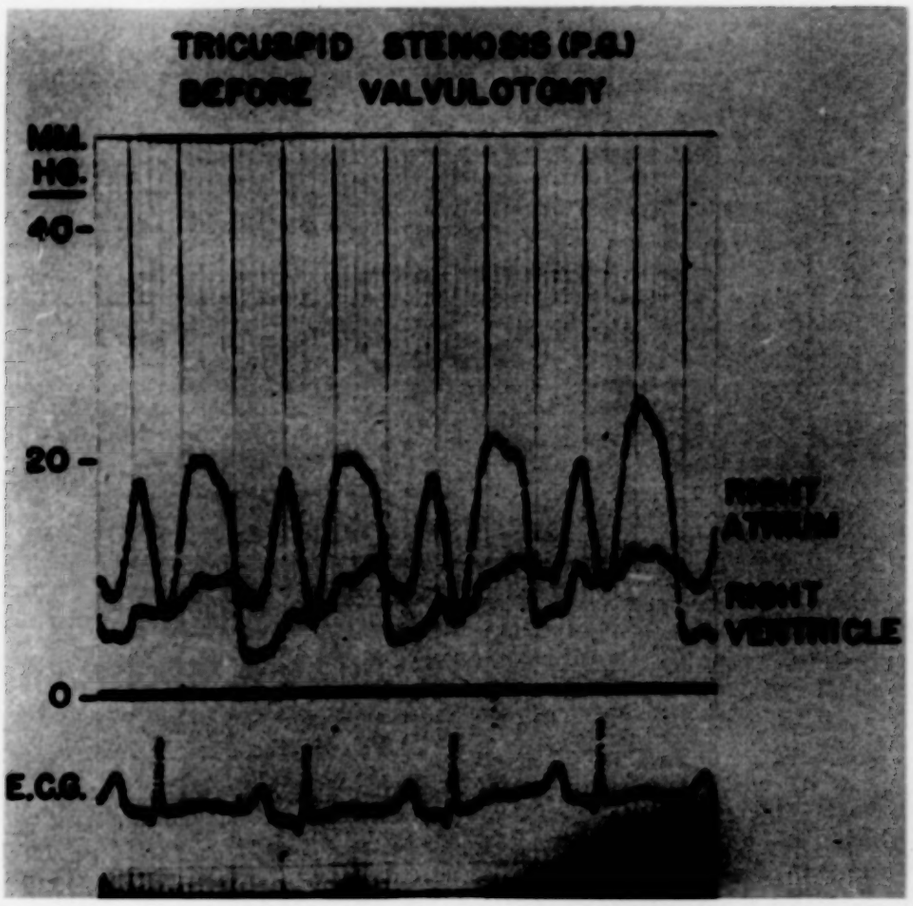


FIG. 7. Double simultaneous pressures in right atrium and ventricle, before valvulotomy.

occasionally seen slight systolic pressure gradients between left ventricle and aorta in the presence of a normal aortic valve.

At the second operation pressure pulses obtained from the right atrium and right ventricle revealed the following: The contour of the right atrial curve (Fig. 6) was essentially the same as that obtained during cardiac catheterization, taking into consideration the more rapid heart rate during surgery. The absolute pressure values, however, were considerably higher (Table 1), the peak of the A wave now being 20 mm. Hg and the mean right atrial pressure 12 mm. Hg. These differences were attributed in greatest part to errors in adjustment of the pressure transducers at the mid-right atrial level at the time of catheterization. The latter level was particularly subject to question as even the x-ray studies failed to reveal the extent of right atrial enlargement.

Of greatest interest were the simultaneous tracings taken from the right atrium and ventricle (Fig. 7) which disclosed a considerable atrioventricular filling pressure gradient, which was large at the beginning of diastole, increased during atrial contraction, and finally dropped to zero just before the onset of ventricular contraction. The diastolic pressure in the right ventricle, which amounted to 3 to 5 mm. Hg at the end of ventricular relaxation, rose during and after atrial contraction to an average of 8 mm. Hg. In other respects the right ventricular pressure pulse was normal, with average peak systolic pressures of 22 mm. Hg.

Further analysis of the right atrial curve in relation to ventricular contraction demonstrates that the early systolic rise in pressure (C wave) is slow and at times delayed in onset; that the subsequent drop in pressure during the "descent of the base" (X-descent) is slight or absent, and greatly delayed, causing the C and V waves to fuse during some beats; that the drop in right atrial pressure after the opening of the tricuspid valve (Y-descent) is a gradual one; and that the

TABLE 1

PRESSURES IN THE RIGHT ATRIUM AND VENTRICLE BEFORE AND AFTER VALVULOTOMY (MM. HG)

	Right Ventricle		Right Atrium		Mean Atrio-ventricular Gradient	Heart Rate	Brachial Artery (cuff)
	Peak systole	End-diastole	Mean	'A' Wave (peak)			
Before valvulotomy	22	8	12	20	6	97	105/80
After valvulotomy	21	8	9	10	1	94	100/85

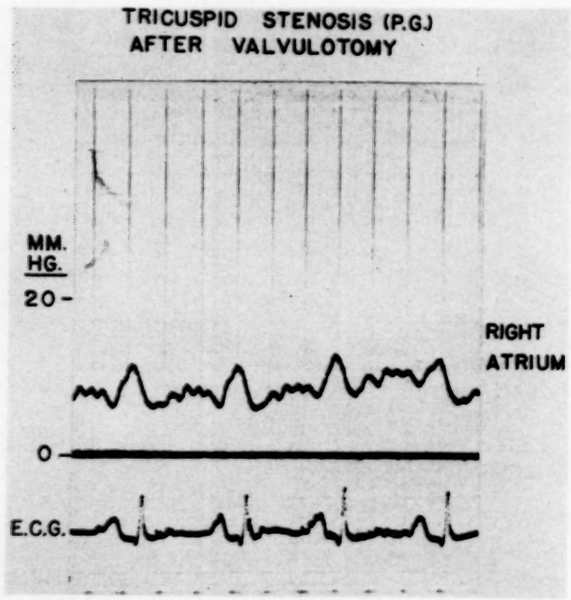


FIG. 8. Right atrial pressure pulse, after valvulotomy. Compare with Figure 6.

highest pressure in the atrium is only 2 mm. Hg below the peak systolic pressure in the ventricle.

After valvulotomy (Figs. 8 and 9) there was a marked drop in the height of the A wave in the right atrial pressure pulse, and a smaller drop in mean right atrial pressure. There was less rise in atrial pressure during ventricular systole. The atrioventricular filling pressure gradient was almost completely abolished.

COMMENTS

Although the presystolic murmur in this patient was heard to the right of the xiphoid cartilage as well as over the apex, it contributed relatively little to the diagnosis of tricuspid stenosis. More important were the evidences of right atrial enlargement in the x-ray and of right atrial hypertrophy in the electrocardiogram, vectorcardiogram, venous and hepatic pulse tracings and the right atrial pressure pulses obtained during catheterization.

It is true that large right atrial A waves and their sequelae are found in other conditions, particularly pulmonary valvular stenosis with or without atrial septal defect; cor pulmonale; some cases of mitral stenosis; and in pulmonary hypertension due to other lesions [*9*]. It has been emphasized by Gibson and Wood [*8*] and by Chesterman and Whitaker [*4*] that giant A waves are only suggestive of tricuspid stenosis in the absence of signs of right ventricular hypertension.

By the same token, the onset of atrial fibrillation in a patient such as this would eliminate many of the features pointing to tricuspid stenosis and the diagnosis could then be made with certainty only by establishing an atrioventricular filling pressure gradient during cardiac catheterization. Failure to enter the right ventricle during cardiac catheterization may be of some importance in pointing to a diagnosis of tricuspid stenosis.

It is of interest to compare the hemodynamic abnormalities in tricuspid stenosis with those encountered in mitral stenosis. In a series of eight cases of mitral stenosis in which simultaneous left atrial, left ventricular and aortic pressures were obtained on the operating table before and after valvulotomy [*10,11*], the mean filling pressure gradients were usually considerably higher than that encountered in the present case of tricuspid stenosis, averaging 13 mm. Hg as compared to 6 mm. Hg. This is mainly a reflection of the higher mean pressures encountered in the left atrium than in the right. On the other hand, the absolute height of the A wave was of the same order of magnitude in the right atrium as in the left.

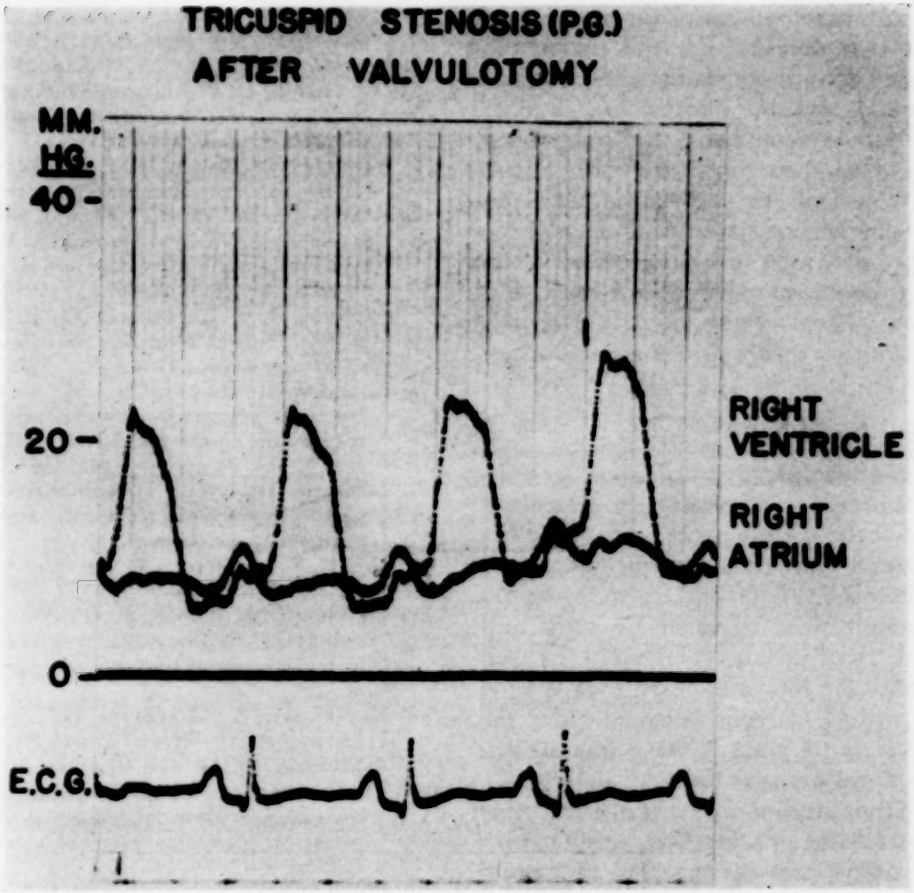


FIG. 9. Same pressures as in Figure 7, after valvulotomy.

It has recently been shown [*12*] that in the normal human heart the Z point pressure in the left atrium and the ventricular end-diastolic pressure are generally higher on the left side than on the right, presumably because of the greater distensibility of the right venoatrial system. However, the absence of any difference in the two atrial pressures at the onset and peak of atrial contraction suggested that right atrial contraction may normally be more vigorous than left atrial contraction.

The present study indicates that right atrial contraction in tricuspid stenosis is much more vigorous and contributes more to ventricular filling than does left atrial contraction in mitral stenosis. This is borne out both by the pressure pulses and by direct observation of the atrial contraction in the exposed heart. These considerations suggest also that the onset of atrial fibrillation may be more serious in tricuspid than in mitral stenosis.

The concept of a pressure gradient across a stenotic valve is a useful one, both for diagnosis and for determining the effectiveness of surgery [*11*]. It should be emphasized, however, that the *mean* filling pressure gradient has the greatest hemodynamic significance. The *maximum* diastolic gradient at any one point may be of little importance, as in a patient without tricuspid stenosis but with giant A waves due to one of the other causes previously mentioned; whereas the present case demonstrates that the gradient at the end of diastole (Z point) may be absent in cases of marked tricuspid stenosis. Similar considerations apply to mitral stenosis with atrial fibrillation and prolonged diastolic periods [*10*].

It should be pointed out that tricuspid stenosis may or may not prevent the development of left atrial hypertension and its concomitant phenomena when mitral stenosis coexists. Several cases have been reported [*4,6*] of proved tight mitral and tricuspid stenosis associated with normal pulmonary artery and "pulmonary capillary" pressures at cardiac catheterization. Apparently the important deciding factors are

the chronologic development of the two lesions and their relative severity. For this reason the finding of a left atrium and pulmonary vasculature of normal size by fluoroscopy, and of normal "pulmonary capillary" and pulmonary artery pressures, does not rule out mitral stenosis in a patient with advanced tricuspid stenosis. In the present state of our knowledge it is probably desirable to obtain pressures on both sides of the mitral valve in such cases, and perhaps even to explore the mitral valve digitally, to insure that severe mitral stenosis is not overlooked.

SUMMARY

A case of uncomplicated tricuspid stenosis, probably rheumatic in origin, is described. The case afforded a rare opportunity to study the clinical and hemodynamic effects of pure tricuspid stenosis.

The diagnosis was suggested by signs and symptoms of right atrial hypertrophy, as well as by a presystolic murmur heard over a wide area. The cardiac catheter failed to enter the right ventricle but a giant A wave was present in the right atrial pressure pulse.

Hemodynamic studies on the operating table before valvulotomy disclosed a mean atrioventricular filling pressure gradient of 6 mm. Hg. After valvulotomy the gradient fell to 1 mm. Hg. Comparison with similar data obtained in patients with mitral stenosis disclosed considerably higher preoperative gradients.

REFERENCES

1. Gorlin, R. and Gorlin, S. G. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *Am. Heart J.*, 41: 1, 1951.
2. Ferrer, M. I., Harvey, R. M., Kuschner, M., Richards, D. W., Jr. and Cournand, A. Hemodynamic studies in tricuspid stenosis of rheumatic origin. *Circ. Res.*, 1: 49, 1953.
3. Trace, H. D., Bailey, C. P. and Wendkos, M. H. Tricuspid valve commissurotomy with a one-year follow-up. *Am. Heart J.*, 47: 613, 1954.
4. Chesterman, J. T. and Whitaker, W. Mitral and tricuspid valvulotomy for mitral and tricuspid stenosis. *Am. Heart J.*, 48: 631, 1954.
5. O'Neill, T. J. E., Janton, O. H. and Glover, R. P. Surgical treatment of tricuspid stenosis. *Circulation*, 9: 881, 1954.
6. Coblentz, B., Dubost, Ch. and Lenègre, J. Retrécissement mitral et retrécissement tricuspidien trâités avec succès par double commissurotomie. *Arch. d. mal. du coeur*, 48: 648, 1955.
7. McCord, M., Swan, H. and Blount, S. G., Jr. Tricuspid stenosis: clinical and physiologic evaluation. *Am. Heart J.*, 48: 405, 1955.
8. Gibson, R. and Wood, P. The diagnosis of tricuspid stenosis. *Brit. Heart J.*, 17: 552, 1955.
9. Grishman, A., Kroop, I. G., Steinberg, M. F. and Dack, S. Presystolic pulsations of the liver in the absence of tricuspid disease. *Am. Heart J.*, 40: 731, 1950.
10. Braunwald, E., Moscovitz, H. L., Amram, S. S., Lasser, R. P., Sapin, S. O., Himmelstein, A., Ravitch, M. M. and Gordon, A. J. The hemodynamics of the left side of the heart as studied by simultaneous left atrial, left ventricular, and aortic pressures; particular reference to mitral stenosis. *Circulation*, 12: 69, 1955.
11. Moscovitz, H. L., Gordon, A. J., Braunwald, E., Amram, S. S., Sapin, S. O., Lasser, R. P., Himmelstein, A. and Ravitch, M. M. The use of simultaneous pressure pulse measurements in evaluating the effect of mitral surgery. *Am. J. Med.*, 18: 406, 1955.
12. Braunwald, E., Fishman, A. P. and Cournand, A. Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. *Circ. Res.*, 4: 100, 1956.

Hemorrhagic Disease in Osteogenesis Imperfecta*

Study of Platelet Functional Defect

BERNARD M. SIEGEL, M.D., IRVING A. FRIEDMAN, M.D. *and* STEVEN O. SCHWARTZ, M.D.

Chicago, Illinois

THE strides made in the understanding of the clotting mechanisms have explained many heretofore unaccountable hemorrhagic phenomena. Perhaps in no phase of the coagulation problem has this been more evident than in platelet function. Progress in this field has been summarized by Stefanini and Dameshek[1] and Ackroyd.[2]

Hemorrhagic disease resulting from platelet dysfunction has been a subject of interest to clinicians and investigators since the original description by Glanzmann[3] in 1918 of a bleeding diathesis attributed to a qualitative platelet defect, or "thrombasthenia." Cases have been reported[4–12] in which the bleeding or the hemorrhagic diathesis was attributed to abnormally functioning platelets. In the group first described by Von Willebrand[13] the vascular factor rather than the platelet factor appeared to be dominant. The functional pathology of the platelet has recently been summarized by Van Creveld,[14] and Soulier and Larrieu[15] in an extensive review have attempted to correlate the clinical and pathophysiologic characteristics of the cases in the literature.

The literature on osteogenesis imperfecta discloses an accompanying bleeding tendency in an occasional case which is usually attributed to a vascular defect; detailed investigations have not been reported, with the exception of Gautier and Guinard-Daniol's case[16] which is compared with our own in the discussion of our report.

We have recently had the opportunity to study a young man with osteogenesis imperfecta, tarda type, who also had a hemorrhagic disease.

CASE REPORT

B. McD., a twenty-five year old white man, was admitted to the Medical Service of the Cook County Hospital, Chicago on January 24, 1955. He had had a rhinoplasty performed two weeks before because of a deformity resulting from a previous nasal fracture, and had had epistaxes in the interval. He had had about thirty mild to moderately severe epistaxes during his life, either spontaneously or associated with minimal trauma. Six episodes of nasopharyngeal hemorrhage had required multiple direct blood transfusions as life-saving measures. One of the episodes was precipitated by head trauma. Transfusions of bank blood had failed to effect hemostasis in those instances. There was a history of repeated fractures. The patient's first fracture occurred at the age of six; osteogenesis imperfecta had been diagnosed at the age of nine. There was also a history of easy bruising. A chronic non-productive cough, unassociated with hemoptysis, had been present for fifteen years. His father, paternal uncle and sister were also known to have osteogenesis imperfecta. The father was separated from his family, so that neither he nor the uncle was available for study.

Physical examination revealed a fairly well developed, alert and cooperative man. There was an increase in the bitemporal diameter of the skull; the forehead was broad, high and rather flat; the occiput was prominent. The scleras were blue. The extremities were long and slender with only minimal bone deformities at the sites of old fractures. There was moderate anterior bowing of both tibias, with some discoloration over the right tibia. Moderate kyphoscoliosis and compensatory emphysema were present.

The significant laboratory findings at the time of the original admission were as follows: red blood cells 3.44 million per cu. mm.; hemoglobin 55 per cent (8.5 gm.); white blood cells 9,700 per cu. mm.; neutrophils 75, bands 6, lymphocytes 12, monocytes 7. The platelets numbered 530,000 per cu. mm. and showed moderate anisocytosis. Reticulocytes were 1.9 per cent of the red blood cells. The red cells showed moderate anisocytosis, slight hypochromia and polychromatophilia. The granulocytes were slightly toxic. Bleeding time was in excess of twenty minutes; coagulation time was ten minutes, thirty seconds; clot retraction was

* From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital. Aided by grants from the Olivia Sue Dvore, Edward Friedman, and Bernice B. Hirsch Foundations.

TABLE I

RESULTS OF BASIC COAGULATION FUNCTION TESTS IN EXAMINATION OF THE PATIENT

Date	Bleeding Time	Rumpel-Leede	Coagulation Time	Recalcified Coagulation Time	Prothrombin Time
1/31/55	Over 20 min.	++++	10 min. 30 sec.	.....	100%
2/10/55	Over 20 min.	++++	11 min. 20 sec.	225 sec.	100%
8/12/55	Over 20 min.	++++	10 min.	250 sec.	100%

normal; prothrombin time was thirteen seconds (100 per cent); the Rumpel-Leede test was strongly positive. Serum non-protein nitrogen, total protein, calcium, phosphorus and gamma globulin values were normal. Marrow, obtained from the iliac crest, was moderately cellular. The megakaryocytes were increased in number and showed many small, "tight" and dark-staining forms; the nucleated red blood cell:white blood cell ratio was approximately 1:2; erythropoiesis was normoblastic; granulopoiesis was moderately "toxic"; a moderate increase in lymphocytes, reticulum cells and plasma cells was noted.

TABLE II

SERUM PROTHROMBIN DETERMINATION*

Date	Determination				
	Serum Prothrombin Time (sec.)	Normal Saline (sec.)	Fresh Plasma (Platelet-poor) (sec.)	$BaSO_4$ Plasma (sec.)	Old Serum (sec.)
1/31/55	20	22	24	35	30
2/10/55	23	27	27	60	43
4/29/55	20	22	20	40	22
8/12/55	22	22	22	22	37
8/19/55	18	19	19	17	19

* Determinations (3 hour) on the dates indicated were performed on whole blood. Additive substances as indicated were mixed with whole blood prior to clotting. The addition of saline provided a control for the effect of dilution. The sources of the additives were different on each occasion and were obtained from patients with a normal serum prothrombin time.

Treatment was conservative during hospitalization. Epistaxes subsided; transfusions were not necessary. Before discharge the red blood cells were 4.21 million per cu. mm.; hemoglobin 71 per cent (11.0 gm.); white blood cells 9,550 per cu. mm.; neutrophils 78, lymphocytes 16, monocytes 3, eosinophils 3 per cent.

The patient's twenty-one year old sister was also examined. She displayed the characteristic stigmata of osteogenesis imperfecta but was otherwise normal. Her bleeding time, coagulation time, Rumpel-Leede test and prothrombin consumption were all within normal limits. She could not be induced to return for a thromboplastin generation study.

To evaluate the patient's bleeding tendency the following studies were performed: Bleeding time, by the method of Duke;[17] coagulation time, according to Lee and White;[18] platelet and reticulocyte counts, modified after Dameshek;[19] Rumpel-Leede test;[20] prothrombin and prothrombin consumption (serum prothrombin) times, after Quick;[21] heparin retardation test (heparin tolerance) of Rosenthal;[22] antithrombin test of Innerfield;[23] recalcified clotting time;[24] thromboplastin generation test, according to Biggs and Douglas.[25]

RESULTS

The bleeding time was consistently prolonged to over twenty minutes. The Rumpel-Leede test remained positive. The coagulation time, the prothrombin time as well as antithrombin and heparin retardation limits were always normal. The recalcified clotting time was consistently borderline abnormal. (Table I.) The serum prothrombin times (prothrombin consumption) were considered abnormal on each of five examinations. In our laboratory, normal values have ranged between forty and eighty-five seconds in over one hundred controls. Only rarely did a control show a serum prothrombin time between thirty-five and forty seconds. There were no control values below thirty-five seconds. Some inconsistencies were noted in the results of the serum prothrombin (consumption) times following the addition of corrective substances (fresh plasma, barium sulfate precipitated plasma, old serum) to our tests. At no time did fresh plasma cause significant correction (allowing for dilution effect) but some variable effect was noted with the other substances. (Table II.)

Using a modification of the technic previously employed by Alexander and Landwehr,[26] Sussman and his coworkers[12] and De Vries and

his associates,[27] and since used by Neeley and his colleagues,[28] a comparison was made of the effect of normal platelets and of the patient's platelets on the prothrombin consumption of a patient with a platelet count of 19,000. This thrombocytopenia was of a secondary (amegakaryocytic) type, resulting from marrow replacement by metastases. (Table III.) The effect of normal platelet suspension and normal platelet-poor plasma on the prothrombin consumption of the patient was also tested. (Table IV.) These studies revealed that the patient's platelets caused little increase in prothrombin consumption in the thrombocytopenic blood; whereas normal platelets corrected the defect. Normal platelets also corrected the abnormal prothrombin consumption of the patient's blood whereas normal fresh platelet-poor plasma had no effect in either case.

TABLE III
EFFECT ON PROTHROMBIN CONSUMPTION*

Additive Substance	3 Hour Serum Prothrombin Time—Tube I (sec.)	3 Hour Serum Prothrombin Time—Tube II (sec.)
Patient's platelets in saline suspension	21	37†
Normal platelets in saline suspension	79	88
Patient's platelet-poor plasma	17	19
Normal platelet-poor plasma	17	17

* Produced by the addition of the platelets of the patient and of a normal control and by the addition of platelet-poor plasma of the same subjects. The substrate is whole blood of a thrombocytopenic patient with abnormal prothrombin consumption.

† This result is mentioned in the text.

The thromboplastin generation test is based on the fact that antihemophiliac globulin (AHG), plasma thromboplastin component (PTC), plasma thromboplastin antecedent (PTA) and normal platelets, when incubated in a wettable test tube in the presence of factors V and VII and Ca^{++}, will produce a potent thromboplastin which can be substituted for preformed thromboplastin in the one-stage prothrombin determination. The generation mixtures were tested at one-minute intervals for eight minutes. The thromboplastin generation curves representative of this test are shown in Figure 1. Of prime importance is the fact that none of the generation mixtures containing the patient's platelets demonstrated significant thromboplastin activity. On the other hand, all combinations in which normal platelets were used with any other components of the patient's blood consistently showed rapid generation of an efficient thromboplastin.

TABLE IV
EFFECT ON PROTHROMBIN CONSUMPTION OF THE PATIENT'S BLOOD*

Additive Substance	3 Hour Serum Prothrombin Time—Tube I (sec.)	3 Hour Serum Prothrombin Time—Tube II (sec.)
Normal platelets in saline suspension	35	109
Normal platelet-poor plasma	17	18

* Produced by the addition of normal platelets and by the addition of normal plasma. The extreme latitude noted is discussed in the text.

COMMENTS

Prior to the introduction of the prothrombin consumption test, cases of "thrombasthenia" could be evaluated only by such relatively insensitive or non-specific technics as coagulation time, bleeding time and estimations of clot retraction.[29] By means of the prothrombin consumption test one could at least implicate the platelets by eliminating the known plasma factors. This test was employed by Van Creveld and Paulssen,[30] Hirsch and his associates[31] as well as by the investigators already cited. Other workers[32] continue to stress possible abnormalities in platelet morphology and agglutinability. By adding platelet suspension to the deficient substrata the effects on clotting time,[33] prothrombin consumption and clot retraction can be observed.

A more specific delineation of platelet functions has also been evolving. Ware and his colleagues[34] have demonstrated a prothrombin accelerator factor as well as a factor accelerating the conversion of fibrinogen in platelet extract. Rapport[35] isolated a vasoconstrictor from platelets which was chemically identified as 5, hydroxytryptamine. Van Creveld and Paulssen[36,37] identified an antiheparin and a thrombo-

plastic factor successively in the phosphatide fraction of platelets. Stefanini and Campbell[38] separated these two factors by absorption methods, and Deutsch[39,40] further identified their physicochemical and physiologic properties. Chemical and physiologic methods for assaying

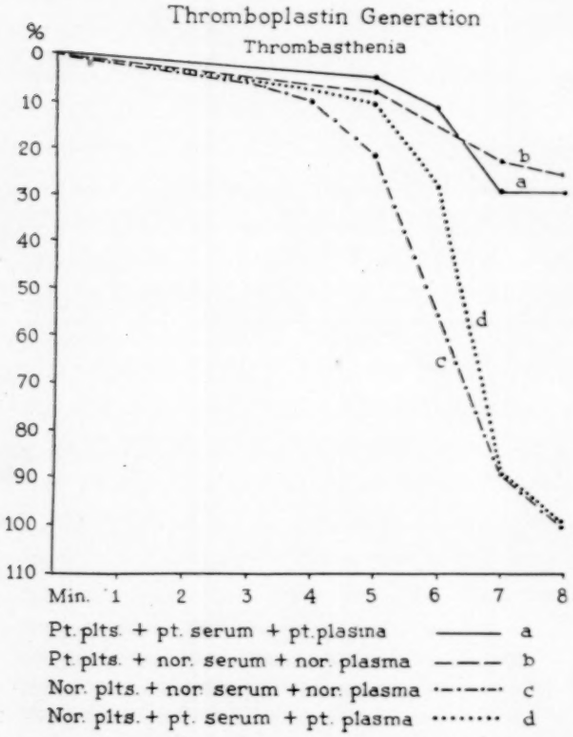


FIG. 1. Representative curves demonstrating the deficiency of thromboplastic function (factor 3) of the patient's platelets.

the platelet vasoconstrictor (serotonin) have also been described.[41,42]

The function of platelets in clot retraction has been indicated by Quick, Shanberge and Stefanini.[43] The work of Fonio[44] attributes this function to the hyalomere portion of the platelets.

The confusion in the identification and delineation of cases characterized by abnormal platelet function has been compounded by the eponymic designations applied to these syndromes before their detailed investigation was possible. One may wonder whether or not such classic syndromes as those of Glanzmann, Von Willebrand, Willebrand-Jurgens and Naegeli will have any meaning as our knowledge expands.

Bernard and coworkers[45] have grouped the thrombopathies into two classes depending on their hemostatic and coagulation function and platelet morphology. One of these groups is characterized by normal coagulation time and clot retractions, abnormal prothrombin consumption and bleeding time. Our case seems to correspond to this group. We do not draw any conclusion from the moderate platelet anisocytosis observed in our study. Their second group is characterized by deficient clot retraction and non-agglutination of platelets but normal prothrombin consumption time.

The clinical manifestations of the hemorrhagic diathesis manifested by the patient are familiar and not uncommon: The ready bruising, the frequent epistaxes and the abnormal bleeding from superficial lacerations. The bleeding may rarely reach magnitude severe enough to require emergent medical care, and detailed study consequently may not be stimulated. Normal bleeding and coagulation times, platelet counts and clot retraction could have tended to rule out the major hemorrhagic diseases in the patient's earlier years. At later examinations a single determination of the serum prothrombin time may not have been definitely abnormal, perhaps falling into the questionable range which we obtained in some of our examinations. (Table II.) It would perhaps have been logical at that time to ascribe such a bleeding tendency to a vascular defect.

Relatively unrefined technics and the complex biologic variables in the reactions themselves account for the variation found when testing for the participating factors in normal hemostasis. Particularly this is true in our attempts to evaluate the production and actions of that substance or group of substances termed "thromboplastin." We were nevertheless able to note the effect of the suspected platelets on prothrombin consumption and on thromboplastin generation.

The thromboplastin generation test has thus far proved to be of greatest value in the analysis of these problems. Its use in evaluating the plasma factors has been well described by Ramot and associates[46,47] and Biggs and Douglas;[23] Soulier and coworkers[48] have indicated its use in evaluating the thromboplastic activity of platelets. The test is difficult and time-consuming but it does provide information not adequately given by other technics. Our use of this technic clearly established a deficiency in the thromboplastic function (factor 3) of the platelets, as shown in Figure 1. The test as performed utilized all possible combinations of normal platelets and patient's platelets, barium sulfate precipitated

plasma, serum and substrate. None of the mixtures in which the patient's platelets were used produced an active thromboplastin efficiently, when compared with controls. The results have been consistent on repeated testing.

The inconsistencies in the serum prothrombin time determinations (Table II) with the addition of various corrective substances has already been noted. If a deficiency of any known plasma coagulation factor existed, fresh plasma should have corrected the defect. This did not occur in our testing. The other reagents were probably at times contaminated with disintegrated platelets or platelet particles. Tables III and IV also show instances of variations in results, only one of which (Table III) reflects on the significance of the findings. The possibility of technical errors is inherent in this procedure, because extensive handling of platelets is required. Repetition of this procedure was not undertaken inasmuch as the thromboplastin generation test is more sensitive and informative.

It would be highly desirable to evaluate the serotonin activity of the patient's platelets when the methods become applicable. A determination of this function might help explain the vascular fragility noted in this case.

The final questions concern themselves with the relationship between the platelet defect and osteogenesis imperfecta, and the significance of the similarity of our case to that of Gautier and Guinard-Daniol.[16] They described a thirteen and one-half month old girl who showed abnormalities of clot retraction whereas the other tests in her coagulation profile were normal. The mother, who is stated to have had blue scleras without osseous disease, presented an abnormal prothrombin consumption test and impaired clot retraction. The father also had abnormal prothrombin consumption and clot retraction. It is unlikely that two such rare conditions as osteogenesis imperfecta and thrombopathy should coexist by chance alone, even though Gautier and Guinard-Daniol believed this to be the case. This concept is understandable since they found no similar concurrence in the literature. We believe, however, that these cases represent congenital defects involving two tissues of mesenchymal origin, the osseous system and the thrombocytes. It also seemed evident that the bleeding tendency in this patient was due, at least in part, to a vascular abnormality. Since we were unable to test the platelets for serotonin activity, we cannot say whether a serotonin deficiency or some intrinsic vascular defect caused the increased capillary fragility. Evaluation of the bleeding tendency in patients with osteogenesis imperfecta by the methods now available should help clarify this point and uncover the precise nature of the platelet and vascular defect.

SUMMARY AND CONCLUSIONS

The case of a young man with osteogenesis imperfecta, tarda type, associated with a hemorrhagic diathesis is presented.

Studies revealed increased capillary fragility, prolonged bleeding time and abnormal prothrombin consumption. His platelets could not correct the prothrombin consumption time of thrombocytopenic blood, and were markedly deficient in producing an active thromboplastin by the thromboplastin generation test of Biggs and Douglas. Normal platelets corrected his abnormal prothrombin consumption and thromboplastin generation. The findings localize the deficiency to the thromboplastic function of his platelets. Whether the increased vascular fragility was due to a deficiency of serotonin or to an intrinsic vascular disease could not be determined.

The development of interest in pathologic platelet function is briefly outlined, and methods for the identification of definite platelet functions, together with tests for their integrity, are described. It is suggested that the clinical syndromes previously associated with "thrombasthenia" will have to be re-evaluated in view of these advances.

Another case of osteogenesis imperfecta associated with functional platelet abnormality has been previously reported. It is probable from the similarities between that case and ours that these two mesenchymal defects are related and not simply coincidental. The bleeding tendency associated with osteogenesis imperfecta has in the past been imperfectly delineated, and therefore more detailed studies in the light of new developments, are warranted when these conditions coexist.

ADDENDUM

The administration of therapeutic doses of cortisone to the patient corrected the Rumpel-Leede test but had no effect on the platelet function as determined by thromboplastin generation. Very recently serotonin levels of the pa-

tient's serum and platelets (kindly performed by Dr. Edward Walaszek, Assistant Professor of Neurophysiology at the University of Illinois College of Medicine) were low before and after cortisone treatment. At this time, we can not draw any definite conclusions from these findings.

Acknowledgments: The authors are indebted to Mr. Frank Higgins and Mr. Braxton Coles for technical assistance.

REFERENCES

1. Stefanini, M. and Dameshek, W. The hemorrhagic disorders, 1st ed., New York, 1955. Grune & Stratton.
2. Ackroyd, J. F. Role of platelets in coagulation, thrombosis and haemostasis with some observations on platelet dysfunction, including thrombasthenia. *Brit. M. Bull.*, 11: 21, 1955.
3. Glanzmann, E. Hereditäre haemorrhagische Thrombasthenie (ein Beitrag zur Pathologie des Blutplättchen). *Jahr. f. Kinderheilk.*, 88: 113, 1918
4. Minot, G. R. A familial hemorrhagic condition associated with prolongation of the bleeding time. *Am. J. M. Sc.*, 175: 301, 1928.
5. Rothman, P. E. and Nixon, N. K. Familial purpura hemorrhagica without thrombopenia. *J. A. M A.*, 93: 15, 1929.
6. Von Willebrand, E. A. and Jürgens, R. Über eine neue Bluterkrankheit, die konstitutionelle Thrombopathie. *Klin. Wchnschr.*, 12: 414, 1933.
7. Bailey, F. R. and McAlpin, K. R. Familial purpura. *Am. J. M. Sc.*, 190: 263, 1935.
8. Cronkite, E. P. and Lozner, E. L. Hereditary hemorrhagic thrombasthenia with severe posthemorrhoidectomy hemorrhage. *U.S. Nav. M. Bull.*, 42: 161, 1944.
9. Imerslund, O. Familial haemorrhagic diatheses with prolonged bleeding time (thrombopathias). *Acta Paediat.*, 34: 315, 1947.
10. Quattrin, N. Beitrag zur Kenntnis der konstitutionellen Thrombopathein. *Acta med. Scandinav.*, 129: 37, 1947.
11. Glanzmann, E. Sporadische konstitutionelle Thrombopathie (Von Willebrand-Jürgens). *Schweiz. med. Wchnschr.*, 76: 1014, 1946.
12. Sussmann, L. N., Wald, N. and Rosenthal, R. L. A hemorrhagic diathesis due to a qualitative platelet defect. *Blood*, 7: 1100, 1952.
13. Von Willebrand, E. A. Hereditäre Pseudohemophile. *Finska läk. sällsk. handl.*, 68: 87, 1926.
14. Van Creveld, S. Functional pathology of platelets. *Acta Haemat.*, 12: 229, 1954.
15. Soulier, J. P. and Larrieu, M. J. Syndrome de Willebrand-Jürgens et thrombopathies. *Rev. hemat.*, 9: 77, 1954.
16. Gautier, P. and Guinard-Daniol, J. Un cas de maladie de Lobstein associee à une thrombasthenie hereditarie et familial de Glanzmann. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 68: 577, 1952.
17. Wintrobe, M. M. Clinical hematology, 3rd ed., p. 262. Philadelphia, 1951. Lea & Febiger.
18. Lee, R. I. and White, P. O. A Clinical study of the coagulation time of blood. *Am. J. M. Sc.*, 145: 495, 1913.
19. Dameshek, W. A method for the simultaneous enumeration of blood platelets and reticulocytes. *Arch. Int. Med.*, 50: 579, 1932.
20. Wright, I. S. and Lilienfeld, A. Pharmacologic and therapeutic properties of crystalline vitamin C. *Arch. Int. Med.*, 57: 241, 1936.
21. Quick, A. J. The Physiology and Pathology of Hemostasis. 1st ed., pp. 125, 142. Philadelphia, 1951. Lea & Febiger.
22. Rosenthal, R. L. Blood coagulation in leukemia and polycythemia. Value of the heparin clotting time and clot retraction rate. *J. Lab. & Clin. Med.*, 34: 1321, 1949.
23. Innerfield, I., Angrist, A. and Benjamin, J. W. Antithrombin titer in acute pancreatitis. *Am. J. Med.*, 12: 24, 1952.
24. Quick, A. J. The diagnosis of hemophilia. *Am. J. M. Sc.*, 201: 469, 1941.
25. Biggs, R. and Douglas, A. J. The thromboplastin generation test. *J. Clin. Path.*, 6: 23, 1953.
26. Alexander, B. and Landwehr, G. Thrombasthenia and thrombocytopenic purpura. *New England J. Med.*, 241: 965, 1949.
27. De Vries, A., Shafrir, E., Efrati, P. and Shamir, Z. Thrombocytopathic purpura with normal prothrombin consumption. *Blood*, 8: 1000, 1953.
28. Neeley, R A., Carson, N. A. J. and Fisher, O. D. Thrombocytopathia hemorrhagica. A case report. *Brit. J. Haemat.*, 1: 234, 1955.
29. Jackson, D. P., Hartmann, R. C. and Conley, C. L. Clot retraction as a measure of platelet function. II. Clinical disorders associated with qualitative platelet defects. *Bull. Johns Hopkins Hosp.*, 93: 370, 1953.
30. Van Creveld, S. and Paulssen, M. M. P. A form of hemorrhagic diathesis characterized by the lack of the third clotting factor, normally present in blood platelets. *Ann. Paediat.*, 181: 193, 1953.
31. Hirsch, E., Favre-Gilly, J. and Dameshek, W. Thrombocytopathic thrombocytopenia: successful transfusion of blood platelets. *Blood*, 5: 568, 1950.
32. Glanzmann, E. Thrombopathien in der ersten Lebenzeit. *Ann. Paediat.*, 178: 449, 1951.
33. De Nicola, P. Thromboplastic factors of platelets. Quantitative and physiopathological evaluation. *Rev. Hemat.*, 9: 536, 1954.
34. Ware, A. G., Fahey, J. L. and Seegers, W. H. Platelet extracts, fibrin formation and interaction of purified prothrombin and thromboplastin. *Am. J. Physiol.*, 154: 140, 1948.
35. Rapport, M. M. Serum vasoconstrictor (serotonin). V. The presence of creatinine in the complex. A proposed structure of the vasoconstrictor principle. *J. Biol. Chem.*, 180: 961, 1949.
36. Van Creveld, S. and Paulssen, M. M. P. Significance of clotting factors in blood platelets in normal and pathological conditions. *Lancet*, 2: 242, 1951.
37. Ibid. Isolation and properties of the third clotting factor in blood platelets. *Lancet*, 1: 23, 1952.
38. Stefanini, M. and Campbell, E. W. Studies on platelets. XII. Isolation and purification of the platelet thromboplastic factor; its physico-chemical

and biological properties. *Rev. hematol.*, 9: 576, 1954.

39. Deutsch, E. Differentiation of certain platelet factors in relation to blood coagulation. *Rev. hematol.*, 9: 483, 1954.
40. Deutsch, E., Johnson, S. A. and Seegers, W. H. Differentiation of certain platelet factors related to blood coagulation. *Circulation Res.*, 3: 110, 1955.
41. Bigelow, F. S. Measurement of platelet-derived vasoconstrictor (serotonin) in normal subjects and patients with hemorrhagic disease. *J. Clin. Invest.* (Abstract), 32: 555, 1953.
42. Zucker, M. B., Friedman, B. K. and Rapport, M. M. Identification and quantitative determination of serotonin (5-hydroxytryptamine) in blood platelets. *Proc. Soc. Exper. Biol. & Med.*, 85: 282, 1954.
43. Quick, A. J., Shanberge, J. N. and Stefanini, M. The role of platelets in the coagulation of the blood. *Am. J. M. Sc.*, 217: 198, 1949.
44. Fonio, A. Ueber die Wirkung des Hyalomers der Thrombocyten auf den Retraktionsvorgang. *Acta Haemat.*, 8: 363, 1952.
45. Bernard, J., Buhot, S., Beaumont, J. L. and Larrieu, M. J. Sur deux types definis de thrombopathies non thrombopenique constitutionelles. *Sang.*, 25: 117, 1954.
46. Ramot, B., Angelopoulos, B. and Singer, K. Plasma thromboplastin antecedent deficiency. *Arch. Int. Med.*, 95: 705, 1955.
47. Ibid. Variable manifestation of P. T. C. deficiency. *J. Lab. & Clin. Med.*, 46: 80, 1955.
48. Soulier, J. P., Larrieu, M. J. and Wartelle, O. La thromboplastinoformation dans les affections plaquettaires. Étude 34 cas a l'aide du test de Biggs et Douglas. *Acta Haemat.*, 14: 160, 1955.

Chronic Erythrocytic Hypoplasia in Adults*

Review of Literature and Report of a Case

SHIH YUAN TSAI, M.D. *and* WILLIAM C. LEVIN, M.D.
Galveston, Texas

THE term "hypoplastic anemia" ("aplastic anemia") denotes by long usage a condition characterized by hypoplasia of all the erythrocytic, myelocytic and megakaryocytic elements in the bone marrow and pancytopenia in the circulating blood. When the hypoplastic process is confined to the erythrocytic series, the bone marrow demonstrates normally proliferating myelocytic and megakaryocytic elements and the resulting anemia is not accompanied by leukopenia or thrombocytopenia. This atypical or unusual form of hypoplastic anemia has been known among children.[1] Its occurrence in adults is rare. Indeed, as a hematologic entity in adults, it has been mentioned in only two of the hematology texts in English.[2,2A] We were able to find twenty-six case reports of this condition in adults, ten of which have been published since 1953, including the one observed by ourselves. These twenty-six cases, all proved by bone marrow biopsy, form the basis of this review. (Table I.)

TERMINOLOGY

Different terms have been applied to this atypical form of hypoplastic anemia. In children, the condition is generally designated "chronic hypoplastic anemia" (of Diamond and Blackfan;[1] Josephs;[6] and Benjamin[5]), "chronic congenital aregenerative anemia,"[3] "congenital hypoplastic anemia"[4,5] or "erythrogenesis imperfecta."[6] The illustrative but ambiguous name, "pure red cell anemia," was first used by Lescher and Hubble.[7] Other terms include "erythrophthisis,"[8] "progressive postinfectious erythrophthisis,"[9,10] "isolated aplastic anemia,"[2] "anerythropoietic anemia,"[11] "(chronic or acquired) erythrocytic hypoplasia (aplasia),"[12–14] "erythroblastophthisis,"[15,16] "essential erythroblastopenia,"[17] "red cell aplastic anemia,"[18] and "(pure or primary) red cell aplasia."[19–21] Pending standardization of the terminology, we choose for the present to use "chronic erythrocytic hypoplasia."

INCIDENCE

Among the twenty-six patients, fifteen were men and eleven were women. The age incidence ranged from twenty (Case No. 8) to sixty-seven years (Case No. 15), with a majority (eighteen patients) in the fifth, sixth and seventh decade of life. Two of the twenty-six patients were Negroids; all the rest were Caucasoids. This condition does not appear to have been noted among the Mongoloids. In Cases No. 13 and 14 in this series the patients were brothers. No occupational or social predisposition was noted.

CLINICAL SYMPTOMATOLOGY

The onset of chronic erythrocytic hypoplasia was insidious. The patients sought medical advice because of symptoms of severe anemia. Their usual chief complaints were general weakness, shortness of breath, lethargy, headache, palpitation, vomiting, anorexia, dizziness, faintness, precordial pain on exertion, amenorrhea, ankle edema and fever. The constant finding on physical examination was pallor; other signs of severe anemia may also be present. Clinical enlargement of the liver was reported in seven patients (Cases No. 4, 13, 15, 16, 23, 24 and 25) and clinical enlargement of the spleen in five patients (Cases No. 4, 13, 16, 23 and 25). The actual incidence of splenomegaly and hepatomegaly as shown at autopsy and surgically was higher. Some authors believe that enlargement of the liver and spleen occurs only after repeat blood transfusion with its complications of hemochromatosis and acquired hemolytic ane-

* From the Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas. Abstract presented at the Southern Section of the American Federation for Clinical Research (Clinical Research Proceedings, 2:113, 1954).

mia.[20,33] While this is true in most instances, there are exceptions. For example, the enlarged spleen found on splenectomy appeared to be a primary feature of chronic erythrocytic hypoplasia in Case No. 14.

HEMATOLOGIC FINDINGS

The distinctive hematologic features of chronic erythrocytic hypoplasia have been succinctly stated by Seaman and Koler[14] as follows: (a) a chronic profound normocytic normochromic or macrocytic normochromic anemia, with decreased or absent reticulocytes; (b) a cellular marrow exhibiting normally active leukocytic and thrombocytic series but marked hypoplasia to virtual absence of nucleated cells of the erythrocytic series; (c) normal differential and usually normal total leukocyte counts, although leukopenia and leukocytosis may occur; (d) normal thrombocyte level and absence of hemorrhagic phenomena; and (e) no extramedullary hemopoeisis. These form the diagnostic criteria for chronic erythrocytic hypoplasia.

The red cells occasionally showed anisocytosis and poikilocytosis (Cases No. 14, 20 and 26). The life span of the transfused normal red cells by the Ashby technic was normal (Cases No. 14, 20 and 24). An increased life span of the chronic erythrocytic hypoplasia patient's own red cells has been suggested[15,16] but laboratory data on this are lacking. The iron utilization as indicated by plasma radioactive iron clearance was reduced (Case No. 14). The Coombs' test was negative (Cases No. 21, 22, 24 and 26). The osmotic fragility of the patient's red cells was normal (Case No. 21). In children with chronic erythrocytic hypoplasia, the presence of "hematogones" (suspected progenitors of the erythrocytic series) in the marrow was a frequent finding.[33] This was not observed in this adult series except possibly in Cases No. 21 and 22, in which small dark "lymphoid" cells were noted in the marrow.[30] In his cases of children with chronic erythrocytic hypoplasia, Cathie noted that red cell maturation fails at the late erythroblastic stage on bone marrow culture.[6] His finding suggests that "maturation arrest" rather than hypoplasia is the pathologic process in chronic erythrocytic hypoplasia. Bone marrow culture studies have not been applied to the adult cases.

A coexistent hemolytic anemia was definitely present in four patients in this series (Cases No. 13, 19, 23 and 25). In these patients, increased hemolytic index, positive Coombs' test, shortened life span of transfused normal red cells by the Ashby technic and shortened life span of the patient's own red cells by radioactive chromium method were noted, but no reticulocytosis was demonstrated. The hemolytic component in Cases No. 13, 19 and 23 apparently followed repeated blood transfusions; but in Case No. 25, hemolysis was claimed to have occurred simultaneously with the selective erythrocytic hypoplasia of the bone marrow.[32]

TABLE 1
TWENTY-SIX CASES OF CHRONIC ERYTHROCYTIC HYPOPLASIA IN ADULTS

Case No.	Year	Authors	Patient's Sex and Age
1.	1922	Kaznelson[8]	M, 58
2.	1933	Kloster[22]	M, 62
3.	1937	Hurst and Kark,[23] Kark[12]	M, 30
4.	1937	Kark[12]	F, 21
5.	1941	Davidsohn[24]	F, 58
6.	1942	Mackey[25]	M, 46
7.	1942	Heilmeyer[5]	M, ?
8.	1942	Moeschlin and Rohr[15]	F, 20
9.	1943	MacFarlane and Currie[26]	M, 24
10.	1943	Strauss[13]	F, 55
11.	1945	Humphreys and Southworth[27]	F, 58
12.	1946	Begemann[16]	M, 59
13.	1951	Loeb et al.[28]	M, 25
14.	1951	Loeb et al.[28]	M, 23
15.	1952	Seaman and Koler[14]	M, 67
16.	1952	Seaman and Koler[14]	F, 40
17.	1953	Chediak et al.[29]	M, 47
18.	1953	Foy and Kondi[18]	M, 46
19.	1954	Tsai and Levin	M, 64
20.	1954	Sakol[20]	M, 51
21.	1954	Chalmers and Boheimer[30]	M, 48
22.	1954	Chalmers and Boheimer[30]	F, 62
23.	1954	Ross et al.[31]	F, 44
24.	1954	Ross et al.[31]	F, 45
25.	1954	Eisemann and Dameshek[32]	F, 58
26.	1955	Fountain and Dale[21]	F, 49

Eosinophilia of the circulating blood and bone marrow was noted in Cases No. 3, 4, 8, 10, 18 and 19. It was believed to be a primary though transient finding of the chronic erythrocytic hypoplasia in Case No. 8 and was used as supporting evidence for the allergic theory of the pathogenesis of chronic erythrocytic hypoplasia.[15] The eosinophilia in Case No. 10 was apparently related to sulfathiazole toxicity. Among the rest of the patients, it appeared to be secondary to treatment such as liver extract

and blood transfusions. Eosinophilia has not been reported to be an integral part of chronic erythrocytic hypoplasia in children.[33,35] Histamine-fast achlorhydria was observed in five patients (Cases No. 4, 12, 17, 19 and 26); but was by no means a constant finding. In fact there are no other characteristic laboratory signs in chronic erythrocytic hypoplasia besides the hematologic ones mentioned previously.

COURSE AND PROGNOSIS

Although one of the refractory anemias, chronic erythrocytic hypoplasia in adults is much less likely to be fatal than the classic type of hypoplastic anemia. In this series, ten patients were reported to be dead; five patients were improved or had maintained blood hemoglobin and red cell levels at the time of the report; and eleven patients were reported to have recovered.

Among the ten patients who died (Cases No. 1, 2, 3, 4, 5, 6, 8, 9, 15 and 19), the life span varied from three weeks (Case No. 1) to eleven years (Case No. 3) with an average of about three years. Transfusion reaction was stated to be the immediate cause of death in Cases No. 3, 4, 8, 9 and 15; and bronchopneumonia or sepsis, in Cases No. 2, 5, 6 and 19. Immediate cause of death was not mentioned in Case No. 1.

Among the five patients reported improved (Cases No. 12, 20, 22, 23 and 24), the maintenance of relatively normal blood hemoglobin and red cell levels was due to repeated blood transfusions in Cases No. 12, 20, 23 and 24; and to ACTH after thymectomy and splenectomy in Case No. 22.

Among the eleven patients reported to be recovered or cured (Cases No. 7, 10, 11, 13, 14, 16, 17, 18, 21, 25 and 26), the recovery was spontaneous in Cases No. 7 and 10. The cure was attributed to thymectomy with removal of benign thymoma in Cases No. 11 and 17; to splenectomy in Cases No. 14 and 25; to ACTH and/or cortisone after splenectomy in Cases No. 13 and 21; to cobalt in Cases No. 16 and 26; and to riboflavin in Case No. 18. It should be noted that the same measures and agents had been used in other patients of this series without such good result. Thus thymectomy with removal of benign thymoma produced only transient or no improvement in Cases No. 21, 22, 23 and 24. Splenectomy alone produced only transient or no improvement in Cases No. 13, 19, 21, 22 and 23. ACTH and/or cortisone after splenectomy resulted in only temporary improvement but no permanent recovery in Cases No. 19 and 22. Cobalt did not elicit an erythropoietic response in Cases No. 19, 20, 21, 23 and 24. Multivitamin preparations containing riboflavin were used in Case No. 19 without any beneficial effect hematologically. Since spontaneous remission and recovery of chronic erythrocytic hypoplasia do occur in adults as well as in children,[6,34–36] critics may raise the point that the reported cures in this series may have been in some instances purely fortuitous rather than due to the therapy. Nevertheless these are the measures that deserve further trial.

To maintain a relatively normal level of blood hemoglobin and red cells, repeated blood transfusions have been the mainstay (for example 290 blood transfusions in nine years in Case No. 3 and 174 blood transfusions in eight years in Case No. 23). With this regimen however are associated all its complications; particularly hemochromatosis, which was noted in half the patients of this series. ACTH and/or cortisone alone, or before splenectomy, appeared to produce either slight or no improvement in this adult series; the result appeared to be somewhat better in children.[37,38] Chronic erythrocytic hypoplasia in this series, as in children, has not been found to respond to the following: iron, copper, arsenic (Fowler's solution), crude liver, stomach preparation, hydrochloric acid, pentnucleotide, ascorbic acid, folic acid, citrovorum factor, liver extract, vitamin B_{12}, multivitamin preparations, thyroid and stilbestrol. The complication of infection was rather frequently seen in this series, but it is difficult to assess the susceptibility as compared with that in normal people and patients with the classic type of hypoplastic anemia. Patients with chronic erythrocytic hypoplasia have normal leukocytic responses to pyogenic infections. It is said that in children chronic erythrocytic hypoplasia appears to play no deleterious role in recovery from infection.[6] This also seems to be true in adults. It is, however, of interest to note that in Case No. 4, a transient episode of agranulocytic angina was precipitated by concurrent mastoiditis and that in Case No. 12, exacerbation of chronic erythrocytic hypoplasia was precipitated by an attack of cholecystitis.

ETIOLOGIC CONSIDERATION

The following varied etiologic factors are suggested for chronic erythrocytic hypoplasia in adults.

Congenital. It has long been implied that chronic erythrocytic hypoplasia in children is of congenital origin. The occurrence of this condition in early infancy without any obvious environmental factor supports this thesis. As chronic erythrocytic hypoplasia may undergo spontaneous remissions or remain stationary, the affected children may reach adulthood with normal physical development.[34,35] Cases No. 13 and 14 (brothers) appear to belong to this category. This may also apply to the other younger patients of this series; but it is difficult to ascribe this defect to the majority of the patients, in whom chronic erythrocytic hypoplasia was not diagnosed until after the fourth decade of life.

Chemicals. Sulfathiazole was definitely incriminated in Cases No. 10, 15 and 16; and benzol in Case No. 7. In all other patients, no history of exposure to such agents was noted. Another case has been reported in which selective erythrocytic hypoplasia followed bismuth and neosalvarsan.[39] As the duration of the erythrocytic hypoplasia in this particular patient was only one week (recovery on cessation of the bismutharsenotherapy and blood transfusion occurred), the case has not been included here.

Benign Thymoma. Seven of the twenty-six patients in this series have been found to have a coexistent thymoma (Cases No. 5, 11, 17, 21, 22, 23 and 24), with one of them also having myasthenia gravis (Case No. 21). Ross et al. have published an excellent review of these cases and have pointed out that the coexistence of benign thymoma and chronic erythrocytic hypoplasia may not be a chance occurrence.[31] They suggest that the conditions are etiologically related in that an endocrine imbalance may be the underlying cause for both; thymoma may be directly responsible for chronic erythrocytic hypoplasia or vice versa. It should be emphasized, however, that benign thymoma is not exclusively associated with chronic erythrocytic hypoplasia but may also occur coincidentally with the classic type of hypoplastic anemia. Ross et al. further suggest that surgical exploration and possibly resection of the thymus be considered in chronic erythrocytic hypoplasia. Inasmuch as the thymus is essentially a prepubertal organ, one would expect it to play an even more important role in chronic erythrocytic hypoplasia in children, but studies in this connection are lacking. Carcinoma of the stomach was present in Case No. 4 and carcinoma of the lung in Case No. 19. It is doubtful whether or not they had any bearing on the causation of chronic erythrocytic hypoplasia; no metastatic lesion was noted in either patient.

Immune Body Reaction and Hypersplenism. Allergy associated with infection and toxin (including chemicals) has been suggested to be the cause of chronic erythrocytic hypoplasia,[9,10,15,16] but there has been no laboratory proof of an immune body reaction in this regard. Smith was the first to demonstrate a definite immune body mechanism in the pathogenesis of chronic erythrocytic hypoplasia by finding isoimmunization by the blood group factor "A" in an infant afflicted with this disorder.[40] In this series, in Case No. 25 simultaneous occurrence of chronic erythrocytic hypoplasia and hemolysis and cure of both after splenectomy was exhibited.[32] Eisemann and Dameshek, who reported this case, suggested therefore than an autoimmune hemolytic mechanism was involved and that a splenic factor acted on the red cell precursors to cause complete inhibition of erythropoeisis. They considered chronic erythrocytic hypoplasia in this case to be a form of (secondary) hypersplenism even though the reticulocytopenia in association with the complete lack of erythropoeisis in the marrow is unique in acquired autoimmune hemolytic anemia and in contradistinction to the usual reticulocytosis and striking erythrocytic hyperplasia.

In support of Eisemann and Dameshek's view that autoimmunization may cause chronic erythrocytic hypoplasia is the report of a similar case in a child by Bonham-Carter, Cathie and Gasser.[41] The fact that ACTH and/or cortisone after splenectomy has effected a permanent cure or temporary recovery in other patients of this series may also be used as partial evidence of immune body reaction and secondary hypersplenism in the pathogenesis of chronic erythrocytic hypoplasia. On the other hand, it has been stated before that the hemolysis in these patients can be secondary to repeated blood transfusions given as treatment for pre-existing chronic erythrocytic hypoplasia. A good example is Case No. 23, in which splenectomy cured the complicating hemolytic component but did not influence the erythrocytic hypoplasia. In the other patient in this series that was cured by splenectomy, Case No. 14, there was no evidence of autoimmunization or hemolysis. Is it to be construed that this case represented an unusual

form of *primary* hypersplenism? The answer is probably no; for if this is the case, then one would expect much higher curative results of splenectomy in chronic erythrocytic hypoplasia than noted in this series of adults and in children.[6,33] To further our understanding, study with splenic extract from patients with chronic erythrocytic hypoplasia would be in order.

Metabolic Defect. Altman and Miller have reported excessive excretion of anthranilic acid (a metabolite of tryptophane) in the urine of children with chronic erythrocytic hypoplasia, suggesting thereby an inborn error of tryptophane metabolism in these patients.[42] Since anthranilic acid is most likely to accumulate under conditions of riboflavin deficiency, these authors administered large doses of riboflavin to children with chronic erythrocytic hypoplasia. But whereas there appeared to be a decrease in the urinary excretion of anthranilic acid with the administration of riboflavin, no change in the hematologic status was reported. These authors also noted that in cases where splenectomy effected improvement in children with chronic erythrocytic hypoplasia, the excessive urinary excretion of anthranilic acid was not reduced. The possible relation between this metabolic defect and chronic erythrocytic hypoplasia thus remains to be clarified.

Of interest in this series is the cure of chronic erythrocytic hypoplasia with riboflavin in Case No. 18, reported by Foy and Kondi.[18] They noted, however, that their patient showed no clinical evidence of riboflavin deficiency and that riboflavin deficiency has not been known to cause generalized or selective hypoplasia of the marrow in patients or experimental animals. The study of anthranilic acid in urine has not yet been applied in this or other adult patients with chronic erythrocytic hypoplasia.

Renal insufficiency. Renal insufficiency with uremia has been known to be associated with selective erythrocytic hypoplasia (and usually also a hemolytic component) in both patients and experimental animals.[43–46] In this series, renal insufficiency has not been incriminated as the primary cause of chronic erythrocytic hypoplasia. In case No. 10 renal infection was present but it was not severe enough to result in renal insufficiency with uremia. In case No. 19 there was terminally severe renal tract infection with uremia and the uremia might have been the exacerbating factor in the end (see case report below). In most cases in this series there was no apparent cause whatsoever. And no common denominator can be readily discerned among the various factors mentioned above.

The disorder of the white blood cell series corresponding to chronic erythrocytic hypoplasia is the "chronic hypoplastic neutropenia" reported by Spaet and Dameshek.[47] In chronic hypoplastic neutropenia there is isolated hypoplasia of the myelocytic series and the resulting neutropenia is generally not accompanied by anemia or thrombocytopenia. It is interesting to note that in four cases of chronic hypoplastic neutropenia, Spaet and Dameshek did not demonstrate a hypersplenic mechanism. That chronic erythrocytic hypoplasia does occur has been used hematologically as an argument in favor of the separate genesis of the erythrocytic, myelocytic and megakaryocytic series (polyphyletic theory of blood formation).[8,15] On the other hand it has been suggested that chronic erythrocytic hypoplasia may begin as an initial total depression of the marrow from which there is recovery of the other series but irreversible damage of the erythrocytic series.[14] Definite proof of this hypothesis is yet to be found. Still others have quoted Nordenson's theory of the functional uniformity of bone marrow and suggest that isolated hypoplasia of the erythrocytic series is not expected to remain long without affecting the other two series.[33] The incidence of chronic erythrocytic hypoplasia terminating in the classic type of hypoplasic anemia in children is not known. In this series only one patient (Case No. 4) also had thrombocytopenia terminally, suggesting hypoplastic involvement of the megakaryocytic series.

It can be noted that most of the factors incriminated in the causation of chronic erythrocytic hypoplasia have also been known to be responsible for the classic type of hypoplastic anemia. Are the two conditions therefore related? Another question to be asked is: Do acute erythroblastopenic crisis and chronic erythrocytic hypoplasia also represent different phases of the same underlying process? As known today, acute erythroblastopenic crisis is by no means a complication only of congenital hemolytic anemias, but may also be caused by most of the etiologic factors previously enumerated,[39,46,48–50] and its duration may be much longer than formerly recognized.[49] The distinction between "acute" and "chronic" is after all artificial. But to answer both questions in the affirmative at present only leads to the new

question of the mechanism of production of one particular type of the three hypoplastic syndromes by the same etiologic agent in different patients.

To summarize, the clinical manifestations of chronic erythrocytic hypoplasia in adults differ little from those in children; but the etiologic factors involved seem to be even more variable in adults. The elucidation of the mechanism of erythrocytic hypoplasia remains a challenging problem.

CASE REPORT

Case No. 19 is reported here as an example of chronic erythrocytic hypoplasia in an adult. The patient, A. G. (unit history No. 14250), a sixty-four year old married white man, was admitted to the Medical Service of the University of Texas Medical Branch Hospitals on December 9, 1952. His presenting symptoms were weakness, shortness of breath, faintness, palpitation, nervousness and loss of weight for some fourteen months. He had been diagnosed to have a severe anemia, with the red cell count as low as one million at one time. Iron, liver extract, folic acid, vitamin B_{12} and multivitamin preparation had been administered without any effect and over forty blood transfusions had been given. His past health had been good except for the usual childhood diseases, influenza (1918) and traumatic amputation of the right thumb (1946). However, since the onset of the present illness, he had had two episodes of pneumonia. He had been an oil field worker, cattle buyer, worker at magnesium plant (World War II) and grocer. He had smoked one package of cigarettes a day for many years. There was no drug habit. In the family history it was noted that his grandfather died of "heart trouble"; tuberculosis was denied.

The physical examination on admission revealed pallor, slight pitting edema of the ankles, reducible right indirect inguinal hernia, absence of vibration sense in the legs, grade 1 benign hypertrophy of the prostate and impaired memory for recent events. The spleen and liver were not felt. There was no jaundice, lymphadenopathy or glossitis. The blood pressure was 130/80.

Laboratory findings: The hemogram revealed the following, red blood cell count 1.09 million per cu. mm., hemoglobin 3.8 gm. per 100 ml., red cell volume 11 ml. per 100 ml., mean corpuscular volume 101 cu. micron, mean corpuscular hemoglobin 35 μg., mean corpuscular hemoglobin concentration 34.6 gm./100 ml., reticulocytes 0 per cent, platelets 171,820 per cu. mm., white blood cell count 6,100 per cu. mm. with 70 per cent neutrophils, 3 per cent eosinophils, 21 per cent lymphocytes and 6 per cent monocytes. Three biopsy specimens of bone marrow were taken from the sternum and the right and left iliac crests; all showed normal cellularity and normal myelocytic and megakaryocytic series, but only a few nucleated erythrocytic elements (megaloblast and erythroblast). The myeloid:erythroid ratio was 65:1. Urinalysis revealed occasional albuminuria, microscopic hematuria, casts and increase of white cells. Gastric analysis after histamine demonstrated achlorhydria. Electrocardiogram showed occasional atrial premature contractions; no definite evidence of myocardial damage. The blood Kolmer and Kahn tests, blood non-protein nitrogen, fasting blood glucose, serum albumin and globulin, cephalin flocculation test, upper gastrointestinal series, barium enema and radiologic bone survey were all within normal limits or negative.

Hospital course: No hematologic response was noted with the following regimen of high protein diet, dilute hydrochloric acid, ascorbic acid, multivitamins, vitamin B_{12} (1,000 μg. in 250 ml. plasma by intravenous infusion), ACTH (20 units intramuscularly every six hours for two weeks) and cortisone (300 mg. as initial dose and gradually reduced to 25 mg. daily for eight days). Twelve pints of whole blood were transfused. The patient was discharged from the hospital on February 14, 1953.

On March 30, 1953, the patient was readmitted for exacerbation of the symptoms of anemia. It was learned that during this interval, a carbuncle of the neck had developed from which he had recovered with penicillin therapy. The physical findings were the same as on the first admission plus noticeable blue-gray pigmentation of the skin. The hemogram revealed a red blood cell count of 1.98 million per cu. mm., hemoglobin 5.3 gm. per 100 ml., reticulocytes 0 per cent, platelets 261,360 per cu. mm., a white blood cell count of 5,400 per cu. mm. with 73 per cent neutrophils, 1 per cent basophiles, 4 per cent eosinophils, 11 per cent lymphocytes and 11 per cent monocytes. A biopsy specimen of the bone marrow showed selective erythrocytic hypoplasia as before (myeloid:erythroid ratio 56:1) and eosinophilia and toxic granulation of the myelocytic elements. Urinalysis revealed occasional albuminuria, microscopic hematuria, urobilinogenuria and bilirubinuria. Fasting blood glucose level was 130 mg. per 100 ml. Serum bilirubin was 1.3 mg. per 100 ml. with 0.67 mg. per 100 ml. of the direct reacting type. Bromsulfalein test showed 20 per cent retention of dye at end of forty-five minutes. A needle liver biopsy specimen of the liver confirmed the clinical impression of hemochromatosis.

After transfusion of ten pints of blood, splenectomy was performed on April 17, 1953. The spleen weighed 390 gm. and the histopathologic diagnosis was congestive splenomegaly. Following splenectomy, the usual leukocytosis and thrombocytosis were noted but there was no increase in reticulocytes and the blood hemoglobin and red cell levels continued to fall. The bone marrow one week after splenectomy showed the same selective erythrocytic hypoplasia as pre-

viously. On April 28, 1953, another course of 1,000 μg. of vitamin B_{12} in 250 ml. of plasma by intravenous infusion was administered without effect. As the anemia became worse, ACTH administration was again instituted May 23, 1953, thirty-four days after splenectomy, this time by intravenous drip of 20 units in 1,000 ml. of 10 per cent glucose in distilled water over an eight hour period daily. On June 9, 1953, the last day of the eighteen day course of the intravenous ACTH therapy, the reticulocyte count was noted to be 7.9 per cent, and on June 12, 1953, it rose to the peak of 17.6 per cent.

A biopsy specimen of the bone marrow on June 12, 1953 revealed marked hyperplasia of the erythrocytic series instead of the previous hypoplasia, and the myeloid: erythroid ratio was 2.2:1. With cessation of ACTH chills, fever (temperatures up to 105°F.), mental confusion, bronchopneumonia, thromphlebitis of the right leg and ulceration at the site of the intravenous drip in the right leg developed. The blood cultures on June 12, 1953 and June 17, 1953 yielded Salmonella schotmülleri. The Salmonella schottmülleri septicemia apparently developed under the masking effect of ACTH, but readily responded to the administration of aureomycin® and streptomycin. By the time of discharge on August 11, 1953, the patient was asymptomatic and blood cultures were negative. On discharge, the red blood cell count was 3.99 million per cu. mm., hemoglobin 13.9 gm. per 100 ml., reticulocyte count 1.4 per cent, platelets 196,000 per cu. mm., white blood cell count 8,500 per cu. mm. with 50 per cent neutrophils, 2 per cent stab forms, 1 per cent basophiles, 13 per cent eosinophils, 22 per cent lymphocytes and 12 per cent monocytes. The follow-up biopsy specimen of bone marrow on September 6, 1953, was normal except for slight plasmocytosis and eosinophilia. The myeloid: erythroid ratio was 3:1. The hemogram and biopsy specimen of the bone marrow were again normal on October 6, 1953.

The patient was then not seen here until September 13, 1955 when he was admitted for the third time. He reported that he had been doing very well during the interval until the spring of 1955, when he started to feel weak and the blood count revealed recurrent anemia. He had again been treated with liver extract, vitamin B_{12} and cobalt without improvement. The chief physical findings were pallor and blue-gray pigmentation of the skin. The red blood cell count was 1.95 million per cu. mm., hemoglobin 5.7 gm. per 100 ml., reticulocytes 0 per cent, red cell volume 18.5 ml. per 100 ml., mean corpuscular volume 95 cu. microns, mean corpuscular hemoglobin concentration 31 gm./100 ml., platelets 460,200 per cu. mm., a white blood cell count of 13,300 per cu. mm. with 65 per cent neutrophils, 3 per cent stabs, 1 per cent metamyelocytes, 1 per cent basophiles, 5 per cent eosinophils, 20 per cent lymphocytes and 5 per cent monocytes. Biopsy specimen of the bone marrow revealed a reversion to the isolated erythrocytic hypoplasia with complete absence of nucleated erythrocytic element. The cellularity was normal and the myelocytic and megakaryocytic elements were normal except for eosinophilia. A hemolytic component was confirmed by the shortened life span of the patient's own red cells by the radioactive chromium method (half life of twelve days). The urinalysis showed some increase of white cells (no urinary symptoms).

On September 15, 1955, two days after admission, the patient complained of substernal pain with radiation to both arms. Serial electrocardiograms confirmed the diagnosis of acute myocardial infarction (anterior) and he was treated for such. In view of the worsening anemia, ACTH (20 units intramuscularly every six hours) was begun on September 21, 1955, despite the myocardial infarction. The hematologic response was the same as on the second admission, the reticulocyte count rose to 17.4 per cent and erythrocytic hyperplasia appeared in the bone marrow on October 7, 1955. Apparently, due to persistence of hemolysis, the anemia was improved without subsiding completely. Then a psychotic reaction (ACTH-induced), urinary tract infection (with non-protein nitrogen rising to 186 mg. per 100 ml.) and Proteus vulgaris septicemia occurred. Supportive treatment and antibiotics were of no avail and the patient died on October 22, 1955.

The autopsy revealed the following findings: Erythrocytic hypoplasia with moderate myeloid and megakaryocytic hyperplasia of bone marrow (apparent reversion to erythrocytic hypoplasia terminally); coronary arteriosclerosis with organizing thrombotic occlusion of the left anterior descending branch; old and recent myocardial infarction of the anterior wall of the left ventricle and the interventricular septum, with mural thrombus in the apex; hypertrophy and dilatation of the left ventricle of the heart; hemochromatosis (weight of liver 2560 gm.); acute necrotizing cystitis, acute pyelonephritis and necrotizing papillitis of kidneys with septicemia (positive blood culture of Proteus vulgaris); active pulmonary tuberculosis in both lower lobes of the lungs; squamous cell bronchogenic carcinoma in right lower lobe at the tuberculous lesion; cortical hyperplasia of the adrenal glands (ACTH therapy); and slight arteriosclerosis of the cerebral arteries. In the opinion of the pathologists, there was no apparent effect of the ACTH therapy on the myocardial infarction, which showed the expected evolutionary change pathologically. The thymus was atrophied and no accessory spleen was found.

ADDENDUM

Since this report was prepared, two additional cases of chronic erythrocytic hypoplasia have been found in the Japanese literature.[51,52]

REFERENCES

1. Blackfan, K. D., Diamond, L. K. and Leister, C. M. Atlas of the Blood in Children. Cambridge, 1944. Harvard University Press.
2. Whitby, L. E. H. and Britton, C. J. C. Disorders of the Blood, 7th ed. New York, 1953. Grune & Stratton.
2A. Wintrobe, M. M. Clinical Hematology, 4th ed. Philadelphia, 1956. Lea & Febiger.
3. Vogel, P., Erf, L. A. and Rosenthal, N. Hematological observations on bone marrow obtained by sternal puncture. *Am. J. Clin. Path.*, 7: 436, 1937.
4. Kohlbry, C. O. Congenital hypoplastic anemia, case report. *J. Pediat.*, 19: 662, 1941.
5. Heilmeyer, L. Handbuch der Inneren Medizin, vol. 2, 4th ed. Berlin, 1951. Springer Verlag.
6. Cathie, I. A. B. Erythrogenesis imperfecta. *Arch. Dis. Child.*, 25: 313, 1950.
7. Lescher, F. G. and Hubble, D. A correlation of certain blood diseases on the hypothesis of bone marrow deficiency or hypoplasia. *Quart. J. Med.*, 1: 425, 1932.
8. Kaznelson, P. Zur Entstehung der Blutplättchen. *Verhandl. d. deutsch. Gesellsch. f. inn. Med. Kong.*, 34: 557, 1922.
9. Barr, H. Postinfectious erythrophthisis. *Folia haemat.*, 35: 111, 1928.
10. Lupu, N. G. and Nicolan, C. T. L'erythrophthisie postinfectieuse progressive. *Le Sang*, 5: 530, 1931.
11. Middleton, W. S. and Meyer, O. C. Marrow insufficiency. *Ann. Int. Med.*, 8: 1575, 1935.
12. Kark, R. M. Two cases of aplastic anemia. *Guy's Hosp. Rep.*, 87: 343, 1937.
13. Strauss, A. M. Erythrocytic hypoplasia following sulfathiazole. *Am. J. Clin. Path.*, 13: 249, 1943.
14. Seaman, A. J. and Koler, R. D. Acquired erythrocytic hypoplasia: a recovery during cobalt therapy (a report of two cases and review of literature). *Acta haemat.*, 9: 153, 1953.
15. Moeschlin, S. and Rohr, K. "Aplastiche Anämie" mit jahrelangen vollständigen Fehlen der Erythroblasten (Erythroblastophthise). *Deutsch. Arch. f. klin. Med.*, 190: 117, 1943.
16. Begemann, H. Über eine isolierte aplastiche Anämie mit vollständigen Fehlen der Erythroblasten (Erythroblastophthise). *Klin. Wchnschr.*, 25: 850, 1947.
17. Hansen, H. G. Über de essentielle Erythroblastopenie. *Acta haemat.*, 6: 335, 1951.
18. Foy, H. and Kondi, A. A case of true red cell aplastic anemia successfully treated with riboflavin. *J. Path. & Bact.*, 65: 559, 1953.
19. Donnelly, M. A case of primary red cell aplasia. *Brit. M. J.*, 1: 438, 1953.
20. Sakol, M. J. Red cell aplasia. *Arch. Int. Med.*, 94: 481, 1954.
21. Foutain, J. R. and Dale, M. Pure red cell aplasia successfully treated with cobalt. *Lancet*, 1: 541, 1955.
22. Kloster, J. Über atypische Anämien. *Folia haemat.*, 51: 251, 1933.
23. Hurst, A. and Kark, R. M. Et tilfelle av aplastik anemi: 290 blodtransfusjoneri lopet avni sekundaer hemochromatose. *Nord. med. tidskr.*, 14: 1285, 1937.
24. Davidsohn, I. Hemochromatosis, thymoma, severe anemia and endocarditis in a woman. *Illinois M. J.*, 80: 427, 1941.
25. Mackey, R. An unusual case of aplastic anemia with organ changes resembling haemochromatosis. *M. J. Australia*, 1: 172, 1942.
26. Macfarlane, J. W. and Currie, J. P. Idiopathic anemia. *Edinburgh M. J.*, 50: 171, 1943.
27. Humphreys, G. H., II and Southworth, H. Aplastic anemia terminated by removal of mediastinal tumor. *Am. J. M. Sc.*, 210: 501, 1945.
28. Loeb, V., Moore, C. V. and Dubach, R. Physiological evaluation and management of chronic bone marrow failure. *Am. J. Med.*, 15: 499, 1953.
29. Chediak, A. B., Fuste, R. and Rosales, G. V. Tymoma y anemia aplastica. *Arch. Hosp. Univ. (Habana)*, 5: 27, 1953.
30. Chalmers, J. N. M. and Boheimer, K. Pure red cell anemia in patients with thymic tumors. *Brit. M. J.*, 2: 1514, 1954.
31. Ross, T. F., Finch, S. C., Street, R. B., Jr. and Strieder, J. W. The simultaneous occurrence of benign thymoma and refractory anemia. *Blood*, 9: 935, 1954.
32. Eisemann, G. and Dameshek, W. Splenectomy for "pure red cell" hypoplastic (aregenerative) anemia associated with autoimmune hemolytic disease (report of a case). *New England J. Med.*, 251: 1044, 1954.
33. Smith, C. H. Hypoplastic and aplastic anemias in infancy and childhood with consideration of syndrome of non-hemolytic anemia of newborn. *J. Pediat.*, 43: 457, 1953.
34. Palmen, K. and Vahlquist, B. Stationary hypoplastic anemia. *Acta haemat.*, 4: 273, 1950.
35. Burgert, E. O., Kennedy, R. L. J. and Pease, G. L. Congenital hypoplastic anemia. *Pediatrics*, 13: 218, 1954.
36. Baar, H. S. Life span of red blood corpuscles in erythrophthisis. *Acta haemat.*, 7: 17, 1952.
37. Gasser, C. Aplastiche Anämie (chronischer Erythroblastophthise) und Cortisone. *Schweiz. med. Wchnschr.*, 81: 1241, 1951.
38. Arrowsmith, W. R. and Segaloff, A. Steroid therapy of congenital aregenerative anemia. Proc. South. Soc. Clin. Research 10th Annual Meeting, 1956.
39. Scharff, O. and Neumann, H. Über eine seltene Form von Knochenmarkschädigung durch Salvarsan. *Med. Klin.*, 40: 500, 1944.
40. Smith, C. H. Chronic congenital aregenerative anemia (pure red cell anemia) associated with isoimmunization by the blood group factor "A." *Blood*, 4: 697, 1949.
41. Bonham-Carter, R. E., Cathie, I. A. B. and Gasser, C. Aplastic anemia (chronic erythroblastophthisis) caused by autoimmunization. *Schweiz. med. Wchnschr.*, 84: 1114, 1954.
42. Altman, K. L. and Miller, G. A disturbance of tryptophane metabolism in congenital hypoplastic anemia. *Nature, London*, 172: 868, 1953.
43. Levin, W. C., Gregory, L., Tsai, S. Y. and Gregory, R. Effects of azotemia on marrow activity. *J. Lab. & Clin. Med.*, 36: 954, 1950.
44. Muirhead, E. E., Jones, F. and Grollman, A. The anemia of renal insufficiency as induced by

bilateral nephrectomy of the rabbit with emphasis on its hemolytic nature. *J. Lab. & Clin. Med.*, 39: 505, 1952.

45. Levin, W. C. and Gregory, L. Hematological effects of uremia. *South. M. J.*, 45: 121, 1952.
46. Richet, P., Alagille, P. and Fournier, E. L'erythroblastopenie aigue de l'anurie. *Presse méd.*, 63: 50, 1954.
47. Spaet, T. H. and Dameshek, W. Chronic hypoplastic neutropenia. *Am. J. Med.*, 13: 35, 1952.
48. Gasser, C. Akute Erythroblastopenie: 10 Fälle aplasticher erythroblasten Krisen mit Riesenproerythroblasten bei allergischtoxischen Zustandsbildern. *Helvet. paediat. acta*, 4: 107, 1949.
49. Seip, M. Aplastic crisis in a case of immune hemolytic anemia. *Acta med. Scandinav.*, 153: 137, 1955.
50. Miesch, D. C., Baxter, R. M. and Levin, W. C. Acute erythroblastopenia: pathogenesis, manifestations and management. *Arch. Int. Med.* (In press.)
51. Morita, H. Various types of aplastic anemia. *Rep. Hemat. Symposium*, 7: 224, 1954.
52. Senda, N. et al. Aplastic anemia of pure type—report of a case and review of literature. *Saishin-Igaku (Newest Med.)*, 9: 354, 1954.

Pulseless Disease*

JANET R. KINNEY, M.D.
Chicago, Illinois

PULSELESS disease is characterized by the absence of pulsations in the carotid and radial arteries. Since this startling physical finding is found in other aortic arch syndromes,[1] it requires a careful differential diagnosis. It may be caused by syphilitic arteritis and, somewhat less commonly, by syphilitic aneurysm. It occurs rarely in dissecting aneurysm and in traumatic injuries of the thorax. When these conditions have been excluded, there remains, as reported from the United States, Great Britain, the Scandinavian countries and Japan, a group of patients consisting predominantly of young and middle-aged women in whom the etiology is unknown. The name, pulseless disease, has been designated for this group.

The following case is interesting in that the evolution of symptomatology was observed over a period of years.

CASE REPORT

This forty-two year old nurse was seen first in April, 1953. An hour prior to admission she had had sudden onset of aphasia with weakness of the left arm and had felt dizzy and nauseated. For the preceding week she had had a very severe headache aggravated by activity and partially relieved by lying down. Two years previously she had had a similar episode of headache and aphasia but with weakness of the right arm.

Physical examination revealed a slight left facial weakness and paresis of the left arm. There was still slight aphasia but it was clearing rapidly. The eyes showed an old alternating left esophoria. The eye grounds revealed normal discs and blood vessels. The pulse in the right arm was weaker than in the left. The blood pressure on the right was 102 mm. Hg systolic and 80 diastolic, on the left 134 systolic and 78 diastolic. The heart was normal in size and contour and the heart tones were clear and distinct. At the base over the right second interspace was a long, loud systolic murmur which transmitted into the right carotid and to a lesser degree into the left. Peripheral pulsations in the legs were normal. Tendon reflexes were hyperactive on the right and decreased on the left.

By the next day the aphasia had cleared completely but the patient complained of blurring of vision on sitting up. The left hand was improving in strength. Further studies included a negative Kahn test, sedimentation rate of 18 mm. per hour (Cutler method) and a normal hemogram and platelet count. The urine had a specific gravity of 1.018 and there were no abnormal findings. The serum non-protein nitrogen was 24 mg. per cent, cholesterol 220 mg. per cent, fasting blood sugar 98 mg. per cent with a flat glucose tolerance curve of 107, 98 and 95 mg. per cent at hourly readings. The electrocardiogram was within normal limits. The x-ray of the chest showed the heart to be normal in size and contour with a rather small aortic knob. Examination by an ophthalmologist confirmed the eye findings.

The patient was discharged on the thirteenth hospital day with a diagnosis of cerebral thrombosis. It was thought that there might be a congenital abnormality of the cerebral vessels since she had had aphasia with the episode of left hemiparesis as well as with the right hemiparesis. On the basis of the murmur, although there was no thrill and no cardiac enlargement, a tentative diagnosis of aortic stenosis was made.

Six months later the patient was admitted to the hospital because of pain in the left arm. She had waked with transient double vision and then noted the onset of a fairly severe aching pain on the inner aspect of the left arm. The nurse who admitted the patient remarked that she was unable to find the right radial pulse. This was confirmed and the blood pressure could not be obtained except for a few indefinite thuds between 90 mm. Hg systolic and 70 diastolic. The blood pressure in the left arm was 130 systolic and 80 diastolic. The pain in the left arm subsided and the absence of the right radial pulse was the only new finding.

The next admission several months later was for chest pain with radiation to the left arm. The patient felt dyspneic but this seemed to be hyperventilation rather than true dyspnea. It was noted that the left radial pulse was becoming more difficult to detect. The possibilities of a dissecting aneurysm or coronary occlusion were considered. However serial electrocardiograms and roentgenograms of the chest showed no change; and no fever, leukocytosis or elevation in sedimentation rate developed.

Throughout the course of the next year there were

* From the Department of Medicine, University of Illinois Medical School, Chicago, Illinois.

seven similar puzzling episodes. Except during these periods the patient was able to continue her supervisory work. Two years after her initial admission her physical findings could be summarized as follows: The right radial pulse could not be palpated. On auscultation, faint sounds could be heard at 100 mm. Hg which faded out at 80. The left radial pulse could not be palpated and no blood pressure reading could be obtained. By the Gaertner maneuver, which consists of raising the arm, applying the blood pressure cuff, inflating the cuff, lowering the arm and releasing the pressure, the flush appeared at 85 mm. Hg which is an approximation of the mean arterial pressure. The carotids were not palpable although the murmur could still be heard in the neck. The femoral, posterior tibial and dorsalis pedis arteries were bilaterally palpable. The blood pressure in the legs was 140 mm. Hg systolic and 100 to 90 diastolic. There had been no change in the electrocardiogram or in the film of the chest.

At this time, with a slowness comparable to the evolution of the syndrome, it was realized that the underlying abnormality must be an occlusive process in the branches of the aortic arch. Similar cases have been reported.

COMMENTS

The diagnosis of pulseless disease is primarily one of exclusion. In this case syphilis could be ruled out. There had been no injury to the chest. Dissecting aneurysm is a possibility but seems unlikely in the presence of a small aortic knob with no enlargement of the aorta in lateral views. Angiography would give valuable information but in view of the possibility of abnormal cerebral circulation it would entail considerable danger.

The symptomatology is predominantly that of occlusion of the internal carotids—headache, vertigo, convulsion, paresis and hemiplegia may occur. Hypersensitivity of the carotid sinus has complicated several cases.

Ocular symptoms are often prominent, but in this case "intermittent claudication of vision" with exercise, and blurring and double vision on arising were the only symptoms. Cataracts, arteriovenous aneurysms and slowing of the arterial circulation have been reported. In Japan the majority of these cases have been reported by ophthalmologists.

Symptoms from occlusion of the radial artery are conspicuous by their absence, due to adequate collateral circulation. This patient had a numb thumb but whether this was central or peripheral was difficult to determine. She complained of fatigue in the arms but there was no detectable atrophy.

Dyspnea, chest pain and tachycardia have been reported. In Jervell's case[2] systolic and diastolic murmurs were heard, and systolic murmurs have been noted in several other reports.

The etiology is unknown. Japanese authors favor a tuberculous arteritis. There are very few postmortem studies on which to base conclusion. Harbitz and Raeder[3] found fibrous thickening and inflammatory infiltration of the vasa vasorum. Frøvig's case,[4,5] showed endarteritis productive proliferans (secondary closure process). There was very little inflammation and mainly a closure process without evidence of primary thrombosis. Trias de Bes and colleagues suggest that the mesenchymal abnormalities observed in the enucleated eye of their case are indicative of a congenital basis for this disease.[6]

Since the etiology is unknown, treatment is unsatisfactory. Long-term anticoagulant therapy has been used. With further advances in arterial surgery a surgical approach, although formidable, might be considered. The patient herein described has been treated symptomatically with papaverine during acute episodes, and priscoline® for the long-term treatment.

SUMMARY

The evolution of a case of pulseless disease is described.

ADDENDUM

This patient died suddenly on November 21, 1956. A postmortem examination was performed six hours later. The significant gross findings were reported as follows.

The aorta showed moderate atherosclerotic changes with calcification and ulceration of a small plaque 2 cm. below the origin of the renal arteries. The innominate artery was patent, but the right common carotid showed an occlusion that began just above its origin. The right subclavian artery showed partial occlusion of its lumen by an apparent subintimal thickening that began at its origin. The left carotid was patent. At the end of the dissection of the left subclavian artery was the beginning of a thick subintimal plaque. All other branches of the aorta were patent and showed minimal sclerotic changes, except for the common iliac arteries which showed moderate sclerotic changes.

The heart showed hypertrophy of the left ventricle and moderate atherosclerosis of the coronary vessels with occlusion of the left coronary artery 1 cm. below its origin. The lungs showed minimal pulmonary edema and slight passive congestion was noted in the liver. The remainder of the organs were essentially normal in appearance. Microscopic sections have not been completed.

REFERENCES

1. Ross, R. S. and McKusick, V. A. Aortic arch syndrome. *Arch. Int. Med.*, 92: 701–740, 1953.
2. Jervell, A. Pulseless disease. *Am. Heart J.*, 47: 780–784, 1954.
3. Harbitz, F. and Raeder, J. G. Ansigts-og øienatrofi. foraarsaget av symmetrisk karotisaffektion. *Norsk mag. f. lægevidensk.*, 87: 529–550, 1926.
4. Frøvig, A. G. Bilateral obliteration of the common carotid artery. *Acta Psychiat. et Neurol.* (Supp. 39), pp. 3–79, 1946.
5. Frøvig, A. G. and Löken, A. C. Syndrome of obliteration of the arterial branches of the aortic arch, due to arteritis. *Acta Psychiat. et Neurol. Scandinav.*, 26: 313–337, 1951.
6. Trias de Bes, L., Sanchez Lucas, J. G. and Ballesta Barcons, F. A case of Takayashu's syndrome: the pulseless disease. *Brit. Heart J.*, 27: 484–488, 1955.

Intrathoracic Meningocele*

A Case Report

RICHARD R. MOYER, M.D., HARRY R. CRAMER, M.D. *and* GARFIELD G. DUNCAN, M.D.
Philadelphia, Pennsylvania

AN intrathoracic meningocele associated with neurofibromatosis (von Recklinghausen's disease) was first reported by Pohl in 1933.[1] Since that time some twenty cases have been reported. According to Laitinen et al.[2] only five of these were diagnosed preoperatively.

FIG. 1. Note café au lait spots, neurofibromas, right kyphoscoliosis (×) and site of second thoracentesis ↑.

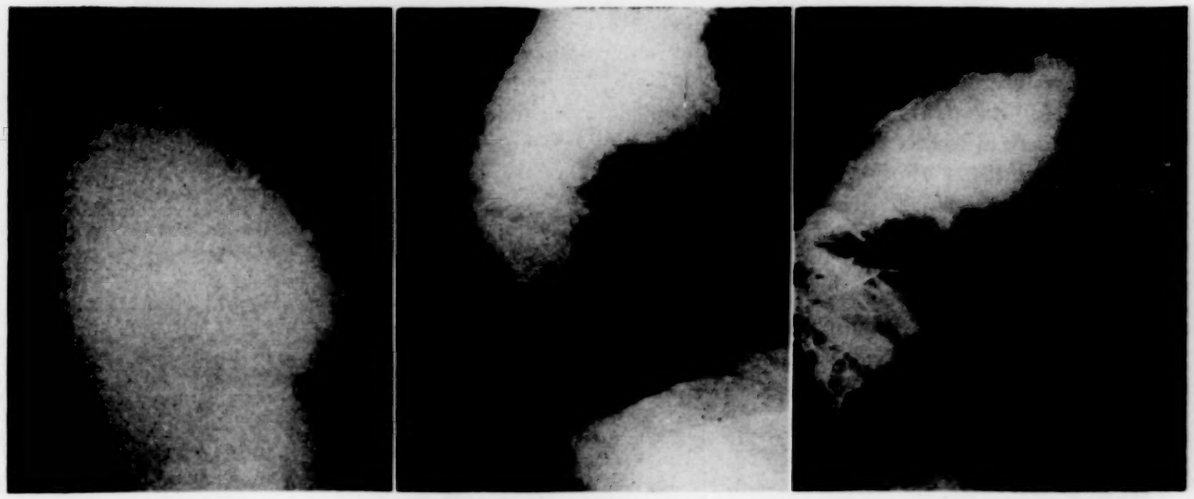
It is our purpose in this paper to add one more case of intrathoracic meningocele associated with neurofibromatosis and complicated by pulmonary tuberculosis; to discuss the diagnosis and methods of treatment; and briefly to discuss the probable pathogenesis of these lesions.

CASE REPORT

T. D. (Unit History No. 11821), a thirty-nine year old white woman, had cutaneous manifestations of neurofibromatosis apparent since birth. There was no family history of the disease. The course was uneventful until the patient was nineteen years of age when, because of progressive kyphoscoliosis, she was admitted to a Philadelphia hospital. A diagnosis of Pott's disease of the spine was made. The patient was asymptomatic following a spinal fusion procedure (in spite of prompt recurrence of her kyphoscoliosis) until the age of thirty-nine, when she complained of headaches of moderate degree. It is significant that the headache was precipitated by coughing. She also suffered from dyspnea on exertion, a symptom which slowly increased in severity and eventually accounted for her admission to the Pennsylvania Hospital six weeks after the onset of these symptoms. Upon physical examination she was found to have multiple "café au lait" spots and cutaneous neurofibromas, a right kyphoscoliosis (Fig. 1) a hydrothorax on the right side (Fig. 2A) and generalized hyperreflexia. A thoracentesis yielded 2,000 cc. of a sterile, straw-colored fluid. A residual radiopaque shadow in the posterosuperior aspect of the right side of the chest was interpreted as due to loculated pleural fluid. (Fig. 2B.) Further attempts at aspiration were unsuccessful. Because of the diagnosis of probable tuberculosis, antituberculous therapy was begun and the patient was discharged to be followed in the outpatient clinic.

Six weeks following her discharge Miss T. D. was readmitted to the hospital because of persistence of the density in the right hemithorax. On the day of her admission it was reported that acid-fast bacilli had been obtained from gastric washings cultured at the time of her previous admission. These organisms were subsequently found to be virulent via guinea pig inoculation. Since it was still believed that the radiopaque area in the right lung field was due to loculated fluid, a needle was inserted in the fourth intercostal space posteriorly approximately 4 cm. from the convexity of the thoracic spine (Fig. 1), and crystal-clear fluid with the appearance and chemical properties of spinal fluid was withdrawn. It was then

* From the Divisions of Internal Medicine, Pennsylvania Hospital, and the Benjamin Franklin Clinic, Philadelphia, Pa.



2A 2B 2C

FIG. 2. (A) the roentgenogram obtained at time of initial admission showing right pleural effusion. (B), roentgenogram taken after the thoracentesis was done shows residual opacity in the posterosuperior region on the right side. (C), myelography, with air as contrast medium, reveals a fluid level within the meningocele.

considered that the roentgen shadow under consideration was due to a meningocele.

Various methods have been used in an attempt to delineate these thoracic lesions: thoracic puncture, alone and with a simultaneous lumbar puncture by which means comparisons in pressure can be observed; thoracoscopy, and myelography with contrast liquid media or air. Transthoracic puncture of these cysts involves the danger of meningitis and, in this instance, the added hazard of tuberculous meningitis. These cysts usually have large patent communications with the subarachnoid space and fill readily with air, making it a simple matter to establish a definite diagnosis. The most efficacious and benign procedure is that of performing air myelography. This was first described in this connection by Cross[3] and subsequently by Laitinen.[2] With the patient in the left lateral decubitus position a total of 80 cc. of spinal fluid was removed via lumbar puncture and replaced by air. Films as shown in Fig. 2C were obtained.

The choice between conservative therapy or operative interference was considered. Sears[4] reported fifteen cases of this type, nine of which were treated surgically. There were four deaths in this group. Surgical correction of these lesions is difficult and is frequently complicated by recurrence of the lesion, leakage of the spinal fluid into the pleural space or meningitis. Baker and Curtis[7] report successful treatment by resection of the lesion in six patients with meningoceles of this type. They believe improved results from surgery in recent years are due to preoperative diagnosis, modern surgical technic and suitable use of antibiotics. They believe that when the lesion is diagnosed preoperatively and the patient is asymptomatic, a conservative course should be followed.

The following factors should influence the selection of therapy for the individual patient: (1) progressive enlargement of the lesion, (2) neurologic symptoms, (3) encroachment upon surrounding structures—vascular, pulmonary or osseous, (4) operative risk, and (5) associated pulmonic disease. Because this patient was considered a poor operative risk, and in view of the mildness of symptoms and the presence of active tuberculous pulmonary disease, conservative therapy was instituted, consisting of antituberculous treatment, close clinical and roentgenologic follow-up, and symptomatic relief.

Several months have elapsed during which this patient has been observed periodically in the out patient department. She continues to be free from symptoms except for intermittent nuchal headaches of moderate degree and low back pain, both of which respond to mild analgesics. No roentgenologic change in the lesion has been detected.

COMMENTS

The controversy over the origin of bone lesions in neurofibromatosis has many facets. Are these lesions part of multiple congenital mesodermal anomalies or are neurofibromas ectodermal in origin initiating bony change by trophic or pressure change? If these lesions are due to expanding neurofibromas, are the neurofibromas intrinsic to bone or in juxtaposition to bone? This raises the controversial question of intrinsic nerve supply to bone. Is there an associated defect in reabsorption of phosphorus by the renal tubules, as suggested by Swann?[8]

Holt[6] has presented an excellent discussion on

this subject. Suffice it to say here that kyphoscoliosis is the most frequent osseous abnormality seen in conjunction with neurofibromatosis; that associated meningoceles are almost always discovered in middle life; that they occur on the convex side of the scoliosis; and that they are associated with vertebral defects at the site of communication with the spinal canal. This would make it appear that they are simply meningeal hernias occurring because of preexisting osseous lesions. While these lesions are rare, their presence should be suspected in all cases of posterior thoracic densities associated with vertebral anomalies, especially in the presence of neurofibromatosis.

SUMMARY

A case of intrathoracic meningocele associated with neurofibromatosis and active pulmonary tuberculosis is presented. The diagnostic measures, probable pathogenesis and therapeutic approaches in this disorder are briefly discussed.

Acknowledgment. We wish to thank Paul A. Bishop, M.D., Director of Roentgenology Department, Pennsylvania Hospital, and Mrs. Sophie J. Kocielski for their counsel and assistance in this undertaking.

REFERENCES

1. Pohl, R. Meningokele in Brustraum unter dem Bilde eines Intrathorakelen Rundschattens. *Röntgenpraxis*, 5: 747, 1933.
2. Laitinen, H. and Turunen, M. Diagnosis of intrathoracic meningocele. *Dis. of Chest*, 27: 547, 1955.
3. Cross, G. O., Reavis, J. R. and Saunders, W. E. Lateral intrathoracic meningocele. *J. Neurosurg.*, 6: 423, 1949.
4. Sears, A. D., Clayton, R. S. and Seebel, E. Intrathoracic meningocele not associated with neurofibromata. *J. Thoracic Surg.*, 26: 101, 1953.
5. Ceglia, P. Intrathoracic meningocele—excision with three and one-half year follow-up. *J. Thoracic Surg.*, 23: 283, 1952.
6. Holt, J. F. and Wright, E. M. The radiologic features of neurofibromatosis. *Radiology*, 51: 647, 1948.
7. Baker, J. M. and Curtis, M. Intrathoracic meningocele. *West. J. Surg.*, 61: 209, 1953.
8. Swann, G. F. Pathogenesis of bone lesions in neurofibromatosis. *Brit. J. Radiol.*, 27, 623, 1954.

". . . there is a somewhat larger group in which definite localization [of the cause of vertigo] may not be possible. . . . Cardiovascular disease may also cause this type of dizziness. . . . The treatment consists of bed rest, sedation and the use of Dramamine . . . ."

Lindsay, J. R.: The Practical Management of Dizziness, California Med. 83:193 (Sept.) 1955.

for dramatic results

Dramamine®

Brand of Dimenhydrinate

SEARLE

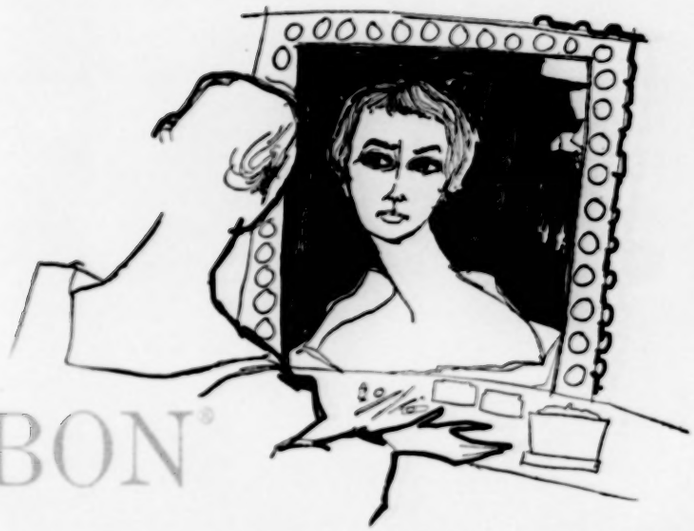
a true
cough specific
non-narcotic

ROMILAR 'Roche'

For suppressing cough, whatever the cause, Romilar is at least as effective as codeine. Yet it has no general sedative or respiratory-depressant activity, and it's remarkably free of side effects such as nausea, constipation, or tendency to habit formation. Available as a syrup, in tablets, or expectorant mixture (with ammonium chloride).

ROCHE *Original Research in Medicine and Chemistry*

Romilar® hydrobromide — brand of dextromethorphan hydrobromide



NEOBON®

TO FIGHT THE INROADS OF AGE

Current opinion stresses the importance of early recognition of the undesirable effects of aging, and adequate metabolic support of the body's fight against them.[1] NEOBON, by providing 4 factors PLUS 1, corrects all 5 of the recognized treatable causes of aging.

Gonadal Hormone Decline—NEOBON'S daily dose of 3 mg. Methyltestosterone and 0.018 mg. Ethinyl Estradiol offsets it.

Hematinic Deficiencies—NEOBON combats nutritional anemia and iron deficiency with essential hematinic factors.

Digestive Enzyme Deficiency—NEOBON supplies pepsin and pancreatin to insure proper absorption and utilization of foods—despite digestive "let-down" of aging.

Nutritional Inadequacy—NEOBON'S complete combination of essential minerals and vitamins replaces deficiencies inherent in the restricted diets of the aging.

PLUS—NEOBON'S new lysine, the amino acid that lifts low value vegetable proteins to the high grade quality found in meat and eggs.

NEOBON in bottles of 60 soft, soluble capsules; prescription only.

1. Klemme, H. L.: Clin. Med., October, 1956.

NEW NEOBON® LIQUID, *a geriatric tonic providing gonadal and thyroid supplementation, improved carbohydrate and protein utilization, hematinic action, and mild antidepressant effect.*

In 16 oz. bottles; prescription only.

PEACE of mind ATARAX®

Roerig Rx

Chicago 11, Illinois

from mild sedation

short-acting

NEMBUTAL

You can achieve any degree of cerebral depression with less short-acting Nembutal—usually only about one-half the dosage of many other barbiturates.

Smaller dosages of short-acting Nembutal mean less drug to be inactivated, shorter duration of effect, little tendency toward hangover.

And with short-acting Nembutal you are using a thoroughly studied sedative-hypnotic with a wide margin of safety.

Abbott

*Nembutal—Pentobarbital, Abbott

to basal anesthesia . . .

701060

from minor abrasions . . .

. . . to major surgery

PSORIASIS

Proved Clinically Effective Oral Therapy—

maintenance regimen may keep patients lesion-free.

COMPLETE LITERATURE AND REPRINTS UPON REQUEST. JUST SEND AN Rx BLANK.

LIPAN®

LIPAN Capsules contain: Specially prepared highly activated, desiccated and defatted *whole* Pancreas: Thiamin HCl, 1.5 mg. Vitamin D, 500 I.U.

Available: Bottles 180's, 500's.

Spirt & Co., Inc.

WATERBURY, CONN.

©Copyright 1956 Spirt & Co.

NEW

Rheumatoid Arthritis

Ataraxoid*

Against Pathogen & Pain

in urinary tract infections

Azo Gantrisin combines the single, soluble sulfonamide, Gantrisin, with a time-tested urinary analgesic - in a single tablet.

Prompt relief of pain and other discomfort is provided together with the wide-spectrum antibacterial effectiveness of Gantrisin which achieves both high urinary and plasma levels so important in both ascending and descending urinary tract infections.

Each Azo Gantrisin tablet contains 0.5 Gm Gantrisin 'Roche' plus 50 mg phenylazo-diamino-pyridine HCl. Gantrisin® - brand of sulfisoxazole

ROCHE | Original Research in Medicine and Chemistry

advanced therapy for advancing hypertension

Apresoline®

hydrochloride

(hydralazine hydrochloride CIBA)

- to lower blood pressure
- to increase renal blood flow
- to decrease cerebral vascular tone

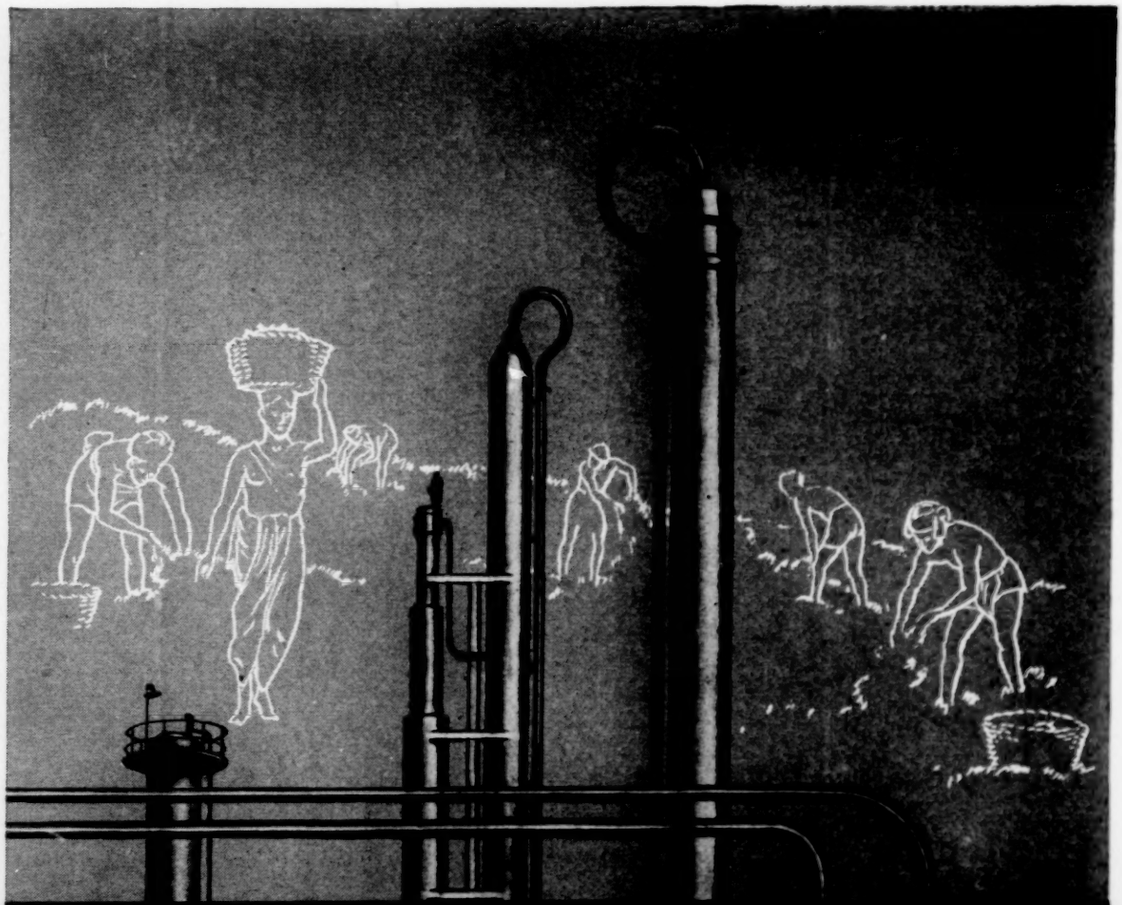
SUPPLIED: Ampuls, 1 ml., 20 mg. per ml.

Tablets, 10 mg. (yellow, double-scored),
25 mg. (blue, coated),
50 mg. (pink, coated);
bottles of 100, 500 and 1000.

Tablets, 100 mg. (orange, coated);
bottles of 100 and 1000.

2/2373MB

CIBA
SUMMIT, N. J.



THE ALKALOID COMPLEX WITH LESS SIDE-EFFECTS

...yet the total activity of RAUWOLFIA

Rautensin provides all the essential antihypertensive alkaloids

Rautensin (the alseroxylon fraction complex of Rauwolfia) contains both rescinnamine and reserpine, together with the other valuable alkaloids.

Produces a gradual and sustained drop in blood pressure.

Calms and soothes the patient without loss of alertness.

Rautensin is less likely to produce mental depression

The alseroxylon fraction complex of Rauwolfia was found less prone to cause mental depression.[1]

Does not usually cause drowsiness.

Is purified and is therefore free of inert dross present in the whole root.

1. Moyer, J.H.; Dennis, E., and Ford, R.: A.M.A. Arch. Int. Med. 96: 530, 1955

Rautensin®

Each tablet contains 2 mg. *purified* Rauwolfia serpentina alkaloids (alseroxylon fraction)

SMITH-DORSEY • Lincoln, Nebraska • a division of The Wander Company

filmtab*

OPTILETS®

THERAPEUTIC FORMULA multivitamins

Each OPTILET *Filmtab* represents:

Vitamin A	7.5 mg. (25,000 units)
Vitamin D	25 mcg. (1000 units)
Thiamine Hydrochloride	10 mg.
Riboflavin	5 mg.
Nicotinamide *(as hydrochloride)*	150 mg.
Vitamin B_{12} *(as cobalamin concentrate)*	6 mcg.
Folic Acid	0.3 mg.
Ascorbic Acid	150 mg.

Supplied: Bottles of 50, 100 and 1000 Filmtabs.

Abbott

*Filmtab: Film-sealed tablets, Abbott; pat. applied for.

they're POTENT

for normal, healthy, comfortable pregnancies

PRECALCIN
Walker
100 CAPSULES
PRECALCIN
A DIETARY SUPPLEMENT
LACTATE
FOR USE DURING PREGNANCY AND LACTATION
EACH CAPSULE CONTAINS
CALCIUM LACTATE Anhydrous 450.00 mg
VITAMIN A Crystalline 2,000 U.S.P. Units
VITAMIN D2 Crystalline 400 U.S.P. Units
THIAMINE HCl 3.00 mg
RIBOFLAVIN 2.00 mg
NIACINAMIDE 10.00 mg
ASCORBIC ACID 30.00 mg
CALCIUM PANTOTHENATE 2.50 mg
PYRIDOXINE HCl 1.00 mg
FOLIC ACID 33 mcg
VITAMIN B12 conc. activity equiv. to 1.00 mcg
FERROUS GLUCONATE 100.00 mg
TRACE ELEMENTS*
*As Adeco Micronutrients
MICRONUTRIENTS
Copper as Copper Sulfate 2 mg. Manganese as Manganese Sulfate 2 mg. Cobalt as Cobalt Sulfate .04 mg. Zinc as Zinc Oxide 2 mg. Magnesium as Magnesium Sulfate 2 mg. Molybdenum as Sodium Molybdate .04 mg. Iodine as Potassium Iodide .02 mg. and Fluorine as Calcium Fluoride .04 mg.
DOSE: 1 capsule three times daily, or as prescribed.
(SEE REAR PANEL)
WALKER LABORATORIES INC
MOUNT VERNON NEW YORK U.S.A.
Walker
100 CAPSULES
PRECALCIN
LACTATE
MOUNT VERNON

PHOSPHORUS-FREE, HIGH-POTENCY DRY-FILL CAPSULES WITH "BUILT-IN" ANTIANEMIA FACTORS

now with FLAVINOL
33.3 mcg. per capsule

Walker LABORATORIES, INC., MOUNT VERNON, N. Y., U. S. A.

STRESSCAPS*

for
resilience
to
stress

ONE OF A COMPLETE LINE OF VITAMIN PRODUCTS
Lederle
FORMULATED UNDER RIGID QUALITY CONTROL FOR YOUR PRESCRIPTION NEEDS

Molehill situations quickly become mountainous to busy persons under persistent stress.

STRESSCAPS replenish the specific vitamin losses sustained by these individuals, increasing their resilience to daily stress, restoring their effic[illegible].

The STRESSCAPS formulation is based on the most recent knowledge regarding the vitamin requirements of the human body under stress.

drg filled sealed capsules

Each Capsule Contains	
Thiamine Mononitrate (B1)	10 mg.
Riboflavin (B2)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B6)	2 mg.
Vitamin B12	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.

Average Dose: 1-2 capsules daily

[illegible] PEARL RIVER, NEW YORK

TO HELP YOUR PATIENTS

(AND YOU . . .)

rest

AND

relax

Niagara

CYCLO-MASSAGE®

Three years of testing in teaching hospitals and medical schools confirms the analgesic, the muscle-relaxant, and the sedative properties of Niagara Cyclo-Massage equipment.

The unique, patented Niagara action is a deep-penetrating, gentle *cycloid*® motion which is widely conducted through the soft tissues of the body to relax many types of muscle spasms and pain associated with such spasms.

For complete details, write or send coupon, today, to Niagara, Adamsville, Pa.

PROFESSIONAL CYCLO-MASSAGE UNITS AVAILABLE THROUGH CYCLOTHERAPY INC., 11 E. 68TH STREET, NEW YORK CITY, N. Y.

© 1956 Niagara Therapy Mfg. Corp., Adamsville, Pa.

Niagara, Dept. AJM-10,
Adamsville, Pa.

Send details on Niagara Cyclo-Massage units.

Name_____

Address_____

CANADA: MONARCH MASSAGE, LTD., FORT ERIE, ONTARIO

two
patients
with
angina pectoris

...your treatment can make *the difference*

In angina pectoris: ". . . the difference between complete, or almost complete, absence of symptoms, or a prolonged illness with much suffering" may lie in routine prophylaxis with Peritrate.[1]

New studies continue to confirm the effectiveness of this long-acting coronary vasodilator. "Impressive and sustained improvement" is observed in patients on Peritrate therapy.[2]

Simple prophylaxis: Peritrate is not indicated to abort the acute attack (nitroglycerin is still the drug of choice). However, you can reduce or eliminate nitroglycerin dependence and provide continuing protection against attacks of angina pectoris with Peritrate. Prophylaxis is simple: 10 or 20 mg. of Peritrate *before meals* and at bedtime. Maintenance of a continuous daily dosage schedule is important for successful therapy.

Peritrate has been demonstrated to prevent or reduce the number of attacks, lessen nitroglycerin dependence, improve abnormal EKG findings and increase exercise tolerance.[3,4,5]

The specific needs of most patients and regimens are met with Peritrate's five dosage forms: Peritrate 10 mg. and 20 mg. tablets; Peritrate Delayed Action (10 mg.) for continuous protection through the night; Peritrate with Phenobarbital (10 mg. with phenobarbital 15 mg.) where sedation is required; Peritrate with Aminophylline (10 mg. with aminophylline 100 mg.) in cardiac and circulatory insufficiency.

Usual Dosage: 10 to 20 mg. *before meals* and at bedtime.

References: **1.** Rosenberg, H. N., and Michelson, A. L.: Am. J. M. Sc. *230*:254 (Sept.) 1955. **2.** Kory, R. C., *et al.*: Am. Heart J. *50*:308 (Aug.) 1955. **3.** Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1953. **4.** Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. **5.** Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

Peritrate®

(brand of pentaerythritol tetranitrate)

WARNER-CHILCOTT

home...

office...

and hospital...

whenever an enema is indicated

FLEET® ENEMA

Disposable Unit

Anatomically correct rectal tube minimizes injury hazard . . . plastic squeeze bottle fits the hand, simplifies instillation . . . effective as soap suds, or more so,(1) FLEET ENEMA induces prompt, spasm-free evacuation.(2)

For home administration and for hospitalized patients prescribe or recommend FLEET ENEMA Disposable Unit . . . extremely effective, too, for pre-examination cleansing in your office . . . available at all pharmacies . . . in use by leading hospitals.

Each 4½ fl. oz. unit contains, per 100 cc., 16 mg. sodium biphosphate and 6 gm. sodium phosphate.

(1) Swinton, N. W., Surg. Clin. of No. Am. 35:833, 1955
(2) Gross, J. M., Jl. Int. Coll. Surg. 23:24, 1955

C. B. FLEET CO., INC.

Lynchburg, Virginia

Makers of Phospho®-Soda (Fleet) • Gentle . . . Prompt . . . Thorough

treat

depression

fatigue

hypochondriasis

- *somatically*
- *psychically*
- *safely*

with *new*

Dexazyme®

For the first time in the treatment of depression, improvement in mentation *and* metabolism *and* mood is now possible with a single therapy—**Dexazyme.**

Dexazyme elevates mood by combining low, *safer* dosages of dextro-amphetamine with Pentrazol.*

Dexazyme improves mentation and clarity of consciousness through action of Pentrazol *and* niacin.

Dexazyme enhances metabolism by providing niacin, thiamine, riboflavin and ascorbic acid.

*brand of pentylenetetrazol

℞ **Dexazyme** #60 Sig.: 1 (or 2) capsules, t.i.d. with meals

GRAY PHARMACEUTICAL CO., INC.
NEWTON 58, MASSACHUSETTS

just one

●

tablet t.i.d.

for your aging patients

may mean the difference between comfort and complaint

"therapeutic bile" **DECHOLIN®**

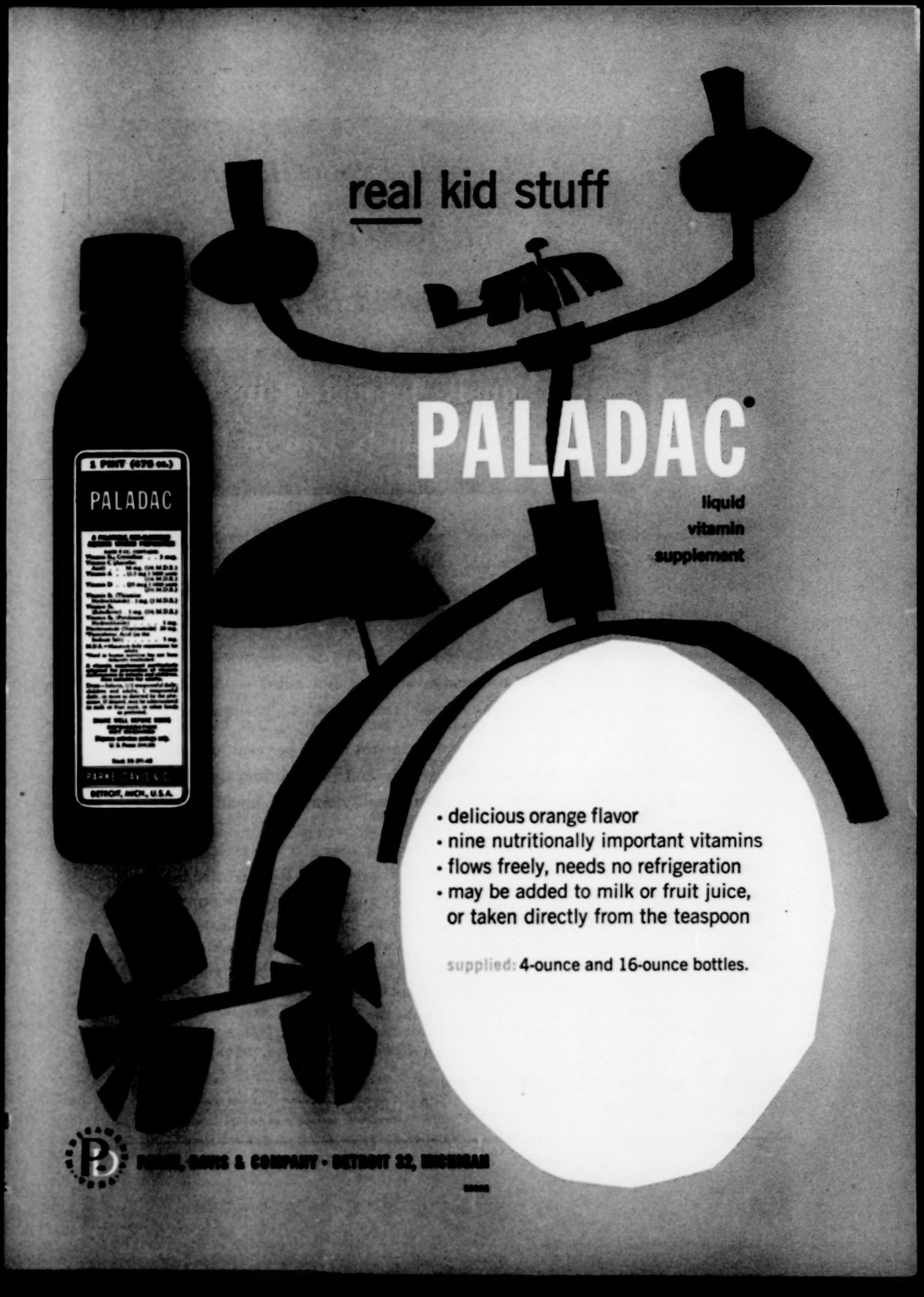
routine physiologic support

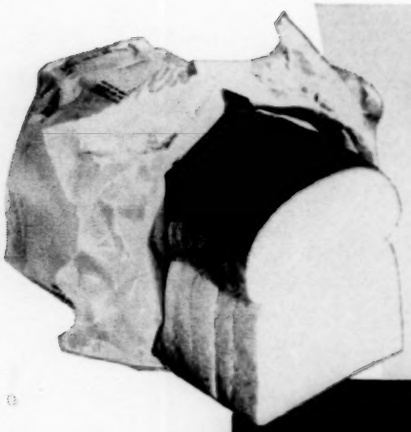
- improves liver and gallbladder function
- corrects constipation without catharsis
- relieves functional complaints of gastrointestinal tract
- enhances medical regimens in hepatobiliary disorders

DECHOLIN Tablets 3¾ gr. (dehydrocholic acid, AMES) and
DECHOLIN SODIUM® Ampuls 20% Solution (sodium dehydrocholate, AMES)

AMES COMPANY, INC • ELKHART, INDIANA
Ames Company of Canada, Ltd., Toronto

23657


real kid stuff
PALADAC®
liquid
vitamin
supplement
1 PINT (473 cc.)
PALADAC
DETROIT, MICH., U.S.A.
• delicious orange flavor
• nine nutritionally important vitamins
• flows freely, needs no refrigeration
• may be added to milk or fruit juice, or taken directly from the teaspoon
supplied: 4-ounce and 16-ounce bottles.
PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN



The Well-Proportioned Nutrients in Enriched Bread

Equally Important in Diets Moderately Low in Fat

The added nutrients in Enriched Bread are chosen qualitatively and quantitatively because of their importance in everyday nutrition. They have proved equally advantageous when dietary adjustment is indicated for therapeutic purposes.

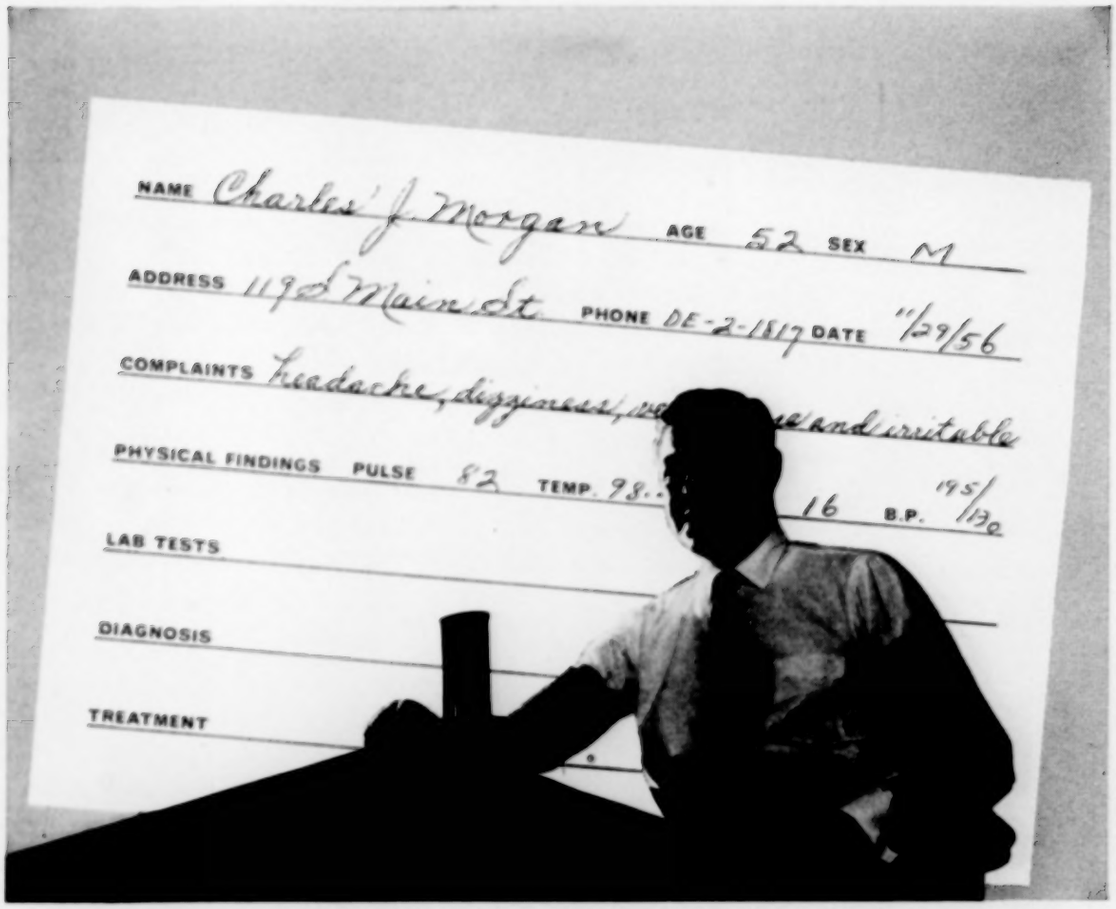
In low-fat diets prescribed for many patients with coronary arteriosclerosis, gallbladder disease, hyperlipemia, obesity, and allied conditions, the proportions of the nutrients in enriched bread are especially significant.

The fat content of enriched bread approximates only 3 per cent, and its cholesterol content is negligible. This feature and, in addition, its well-balanced proportions of essential nutrients qualify enriched bread as an important constituent of low-fat diets.

Six slices of the average enriched bread, containing 4 per cent added nonfat dry milk, provide 12 grams of good quality protein (flour protein supplemented with milk protein), 0.36 mg. of thiamine, 0.26 mg. of riboflavin, 3.35 mg. of niacin, 3.5 mg. of iron, and 126 mg. of calcium—from 16 to 29 per cent of the adult patient's daily needs for each of these nutrients. Yet six slices of enriched bread supply only 19 per cent of the nutrient energy of a 2,000-calorie diet.

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.



Start all your hypertensives on **RAUVERA®**

for grcater **SAFETY**

Safety is a distinguishing feature of *Raurera*, a potent antihypertensive agent with safeguards inherent in the purified mixed alkaloid fractions, alseroxylon (1 mg. per tablet) and alkavervir (3 mg. per tablet). The risks of depression, postural hypotension or reduction of blood pressure to undesirable levels are virtually absent with *Raurera*. Patients can be started routinely on *Raurera*, and therapy can be continued over long periods of time.

More EFFECTIVE therapy Alseroxylon and alkavervir combined are much more effective than either drug used alone. The resulting additive if not synergistic action provides full antihypertensive effects with relatively smaller doses of each drug and with fewer side actions.

SMITH-DORSEY · Lincoln, Nebraska · a division of The Wander Company

gentle is the word

for Noludar

Mild, yet positive in action, Noludar 'Roche' is especially suited for the tense patient who needs to relax and remain clear-headed— or for the insomniac who wants a refreshing night's sleep without hangover. Not a barbiturate, not habit-forming. Tablets, 50 and 200 mg; elixir, 50 mg per teasp.

Noludar® brand of methyprylon (3,3-diethyl-5-methyl-2,4-piperidinedione)

ROCHE

Original Research in Medicine and Chemistry

who coughed?

WHENEVER
COUGH THERAPY
IS INDICATED

Hycodan

ENDO LABORATORIES INC

Endo

ELECTRODYNE PM-65 with *Electrocardioscope**

**optional*

A PROVEN INSTRUMENT THAT:

- Detects and treats cardiac arrest automatically.
- Provides continuous visual display of electrocardiogram.
- Provides immediate recognition of any cardiac arrhythmia.

The 3 flat E. C. G. disk electrodes held on chest by rubber strap, afford simple, fast, external hookup.

Your Inquiries for Technical Information, Literature, and Prices Invited...

SPECIALISTS IN ELECTRODYNE MEDICAL ELECTRONICS

ELECTRODYNE CO., INC.
90 ENDICOTT STREET
NORWOOD, MASSACHUSETTS, U.S.A.

With the addition of the new Electrocardioscope, the Electrodyne PM-65 boasts a refinement that is unlike any other instrument of its kind available today. The PM-65 with scope now provides a continuous visual display of the electrocardiogram and immediate recognition of any cardiac arrhythmia.

As you know, the Electrodyne PM-65 is a combination of two proven instruments — the reliable Cardiac Monitor and the well documented Cardiac Pacemaker (developed in conjunction with Paul M. Zoll, M. D.). When attached to the patient it will instantly signal cardiac arrest and automatically provide effective external stimulation to the dormant heart at the very onset of cardiac arrest.

Other important Electrodyne instruments are: The Cardiac Pacemaker, the Cardiac Defibrillator, the Cardiac Alarm, the *External* Defibrillator and combinations of these units.

"Mediatric" will help make the "senior" years more pleasant and enjoyable.

"Mediatric" is specially formulated to counteract the adverse influence of declining gonadal function, nutritional inadequacy and emotional instability.

"Mediatric" contains estrogen and androgen in amounts that will effectively supplement reduced gonadal hormone production; nutritional supplements carefully selected to meet the needs of the patient; and a mild antidepressant to promote a brighter mental outlook. Available in tablets, capsules, and liquid.

"MEDIATRIC"®

Steroid-Nutritional Compound

IN PREVENTIVE GERIATRICS

Ayerst

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

5660

Meat...

and the Need for Reasonable Amounts of Fat to Maintain Good Health

The place of dietary fat in human nutrition is being widely discussed. Scientists who know tell us that some fat is desirable in our everyday diet whether body weight has to be reduced or not.

Why are fats important to good health? Because they contribute to the processes of growth and replacement of tissue. Because they are an important source of calories. Because they make foods more inviting and better tasting.

Despite great advances in nutritional knowledge the exact role of fat in the diet is not yet fully defined. Yet it is known that some fat is necessary in healthful day-to-day nutrition.

For good health, good nutrition, and tastier meals, be sure there is some fat—in reasonable amounts—in your daily diet. Meat—the most versatile of high protein and B vitamin foods—because of its many varieties and cuts is an excellent vehicle to provide this essential fat in any amount desired. Animal fat products, such as lard, are not only economical, but add delightfully to the taste appeal of hundreds of recipes.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute

Main Office, Chicago... Members Throughout the United States

Life without Frenzy

He used to fuss and fume when traffic slowed him down. Now he relaxes—his pace of living has been "calmed down"—since his doctor prescribed

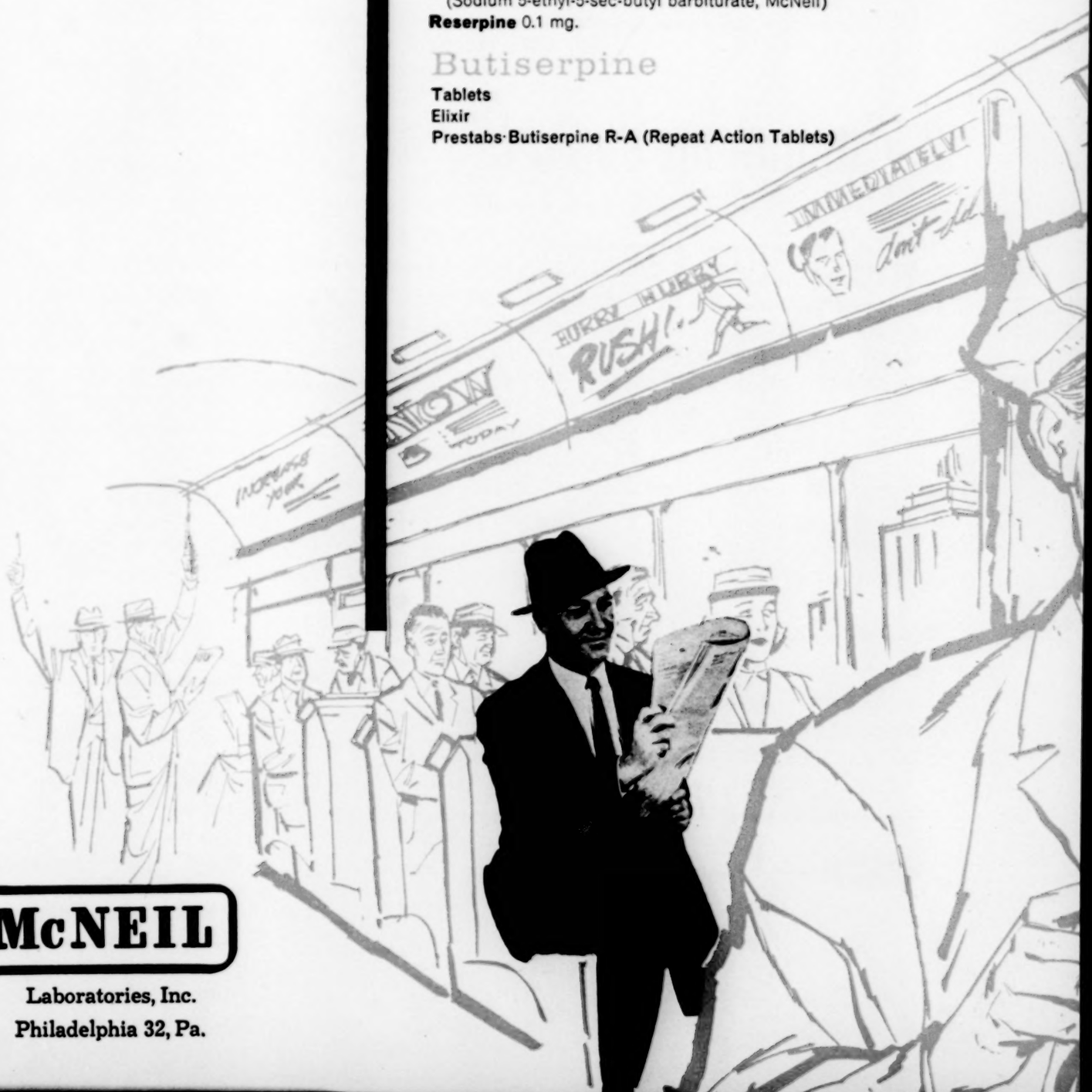
Butiserpine®

That's the tranquilizing-sedative-hypotensive effect BUTISERPINE has on tense, highstrung patients. Its *Butisol* component quickly induces a more reasonable, tranquil attitude. This gives the *reserpine* component a chance to build up to its maintenance tranquilizing effect.

Now you can prescribe Butiserpine also in its delightful Elixir form. Each tablet or teaspoonful of elixir contains:

Butisol® Sodium 15 mg. (¼ gr.)
(Sodium 5-ethyl-5-sec-butyl barbiturate, McNeil)
Reserpine 0.1 mg.

Butiserpine
Tablets
Elixir
Prestabs·Butiserpine R-A (Repeat Action Tablets)



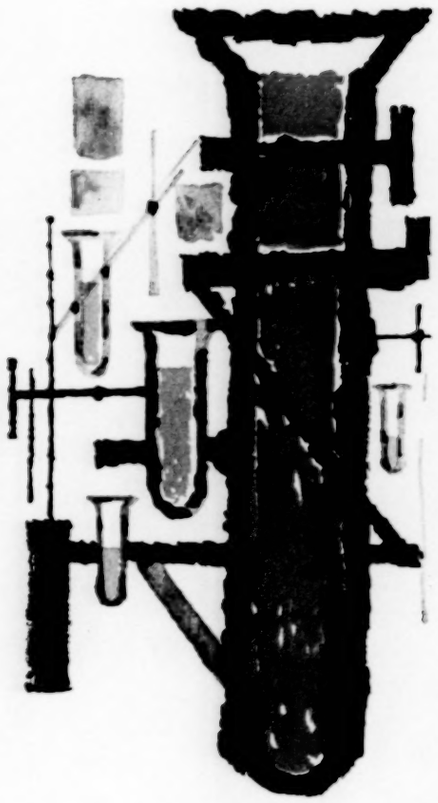
McNEIL

Laboratories, Inc.
Philadelphia 32, Pa.

PRONEMIA*

HEMATINIC LEDERLE

minimum dosage
maximum response



dry filled sealed capsules

High potency dosage of every known hemopoietic factor, offered in a most easily assimilable form for all treatable anemias, including maintenance of pernicious anemia patients.
Dosage is only one capsule daily

Each capsule contains:

Vitamin B_{12} with Intrinsic Factor Concentrate	1 U.S.P. Oral Unit
Vitamin B_{12} (additional)	15 mcgm.
Powdered Stomach	200 mg.
Ferrous Sulfate Exsiccated	400 mg.
Ascorbic Acid (C)	150 mg.
Folic Acid	4 mg.

When divided dosage of this formula is preferred prescribe PERIHEMIN* *Hematinic, 3 capsules daily*

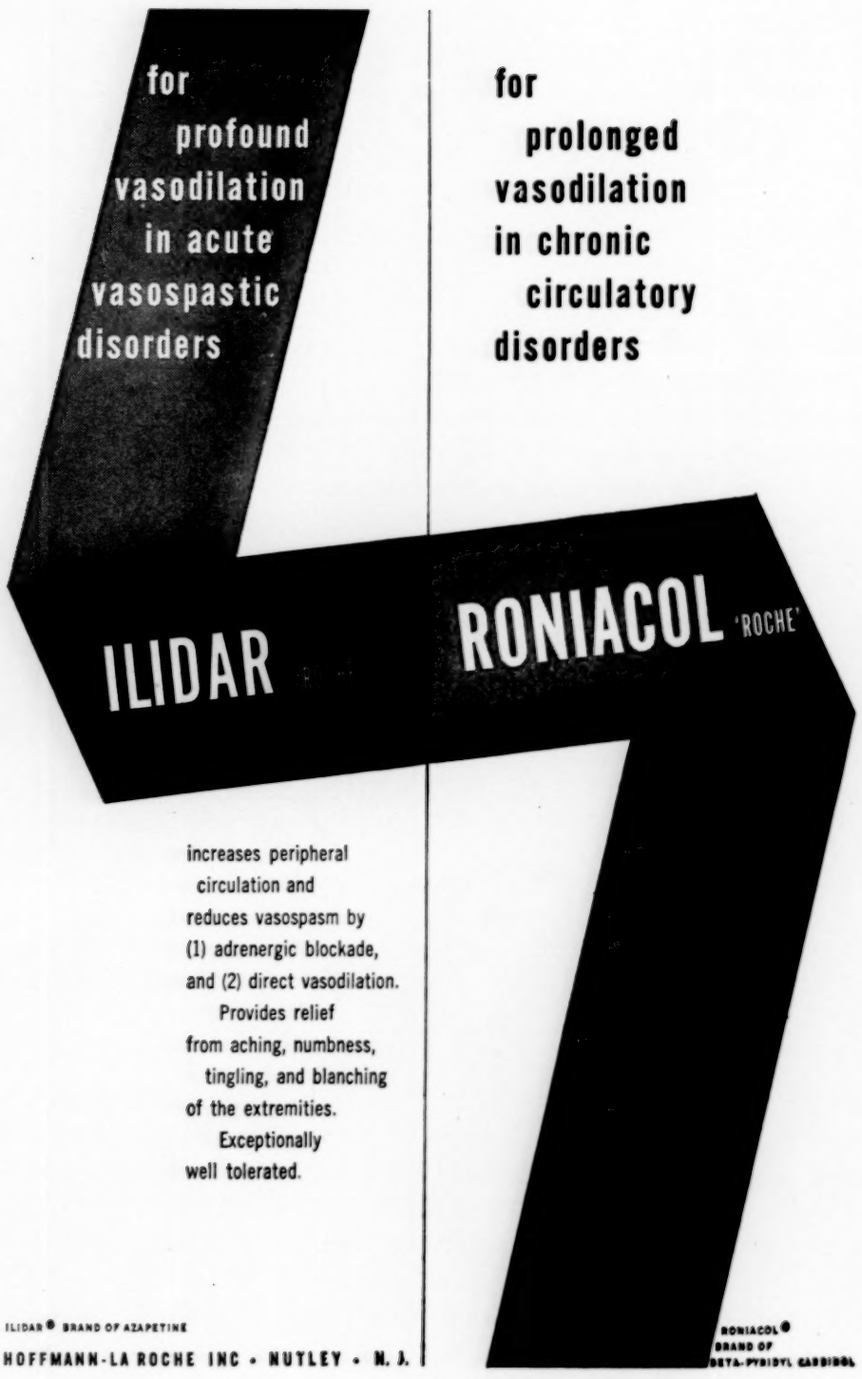
Lederle LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, N. Y.

*Reg. U. S. Pat. Off.

Advertisers Index

February 1957

Abbott Laboratories . . . . . 16–17, *Insert Facing Page* 56, 57, 68, 75
American Bakers Association 84
American Meat Institute 90
Ames Company, Inc. 4, 82
Armour Laboratories 33
Ayerst Laboratories 89
Burroughs Wellcome & Co., Inc. 11
Ciba Pharmaceutical Products, Inc. . . . . 22, 73, *Fourth Cover*
Corn Products Refining 52–53
Eaton Laboratories 69
Electrodyne Co., Inc. 88
Endo Laboratories, Inc. 87
Geigy Company 42
C. B. Fleet Co., Inc. 80
Gray Pharmaceutical Co. 81
Hoffmann-La Roche Inc. . . . . 30, *Insert Facing Page* 40, 66, 72, 86, 94
Lakeside Laboratories, Inc. 47
Lederle Laboratories 26, 38, 45, 50, 56, 77, 92
Thos. Leeming & Co., Inc. 28
Eli Lilly and Company 64
S. E. Massengill Company 10, 27, 43
McNeil Laboratories, Inc. 60–61, 91
Mead Johnson 58
Merck Sharp & Dohme 14, 25, 34, 46, 63
National Drug Co. 32
Niagara Therapy Mfg. Corp. 78
Organon Inc. 6
Parke, Davis & Company 15, 28, 40–41, 50, 83
Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc. 23, 35, 55, 71
Riker Laboratories Inc. . . . . 12–13, 24, 44, *Third Cover*
A. H. Robins Co., Inc. 51
J. B. Roerig Co. 19, 36–37, 67
G. D. Searle & Co. 65
Sherman Laboratories 54
Spirt & Co., Inc. 70
E. R. Squibb & Sons, Division of Mathieson Chemical Corp. 8, 18, 31, 48–49, 59
Varick Pharmacal Company, Inc. 39
Walker Laboratories, Inc. 76
Wallace Laboratories 62
Wander Company, Division of Smith-Dorsey 74, 85
Warner-Chilcott Laboratories 1, 79
Winthrop Laboratories 2
Wyeth Laboratories 20–21, 29, 40


for profound vasodilation in acute vasospastic disorders
for prolonged vasodilation in chronic circulatory disorders
ILIDAR
RONIACOL 'ROCHE'
increases peripheral circulation and reduces vasospasm by (1) adrenergic blockade, and (2) direct vasodilation.
Provides relief from aching, numbness, tingling, and blanching of the extremities.
Exceptionally well tolerated.
ILIDAR® BRAND OF AZAPETINE
HOFFMANN-LA ROCHE INC • NUTLEY • N. J.
RONIACOL® BRAND OF BETA-PYRIDYL CARBINOL

Medihaler

Means self-powered, uniform, measured-dose inhalation therapy . . . made possible by specially designed metered-dose valve . . .

Medihaler

Means notably safe and effective therapy when indicated for children. Medication is in leakproof plastic coated bottles . . .

Medihaler

Means true nebulization. Each measured dose provides 80 per cent of its particles in the optimal size range—0.5 to 4 microns radius—insuring effective penetration of the respiratory tract.

Medihaler

Medication and Adapter fit into neat plastic case, convenient for pocket or purse . . .

Medihaler

Means an unbreakable Oral Adapter—no movable parts—no glass to break—no rubber to deteriorate . . .

Medihaler

Means greater economy—no costly glass nebulizers to replace, and one or two inhalations usually suffices for prompt relief.

[redacted]

In Asthma

For Rapid Relief of Acute or Continuing Bronchospasm

Medihaler-Epi™

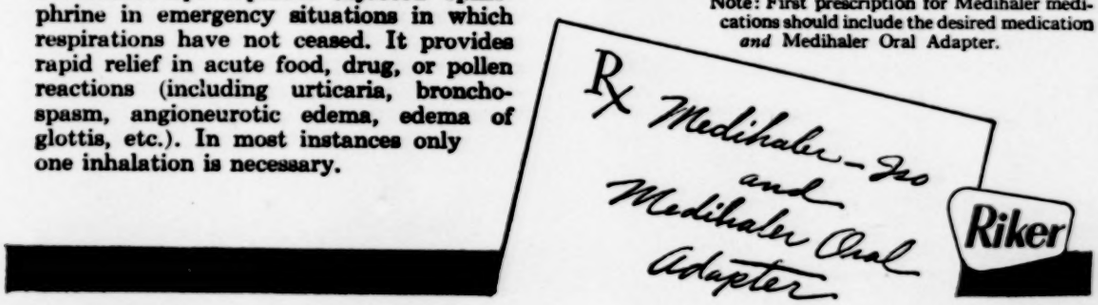
Riker brand of epinephrine 0.5% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.125 mg. epinephrine. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Medihaler-Epi replaces injected epinephrine in emergency situations in which respirations have not ceased. It provides rapid relief in acute food, drug, or pollen reactions (including urticaria, bronchospasm, angioneurotic edema, edema of glottis, etc.). In most instances only one inhalation is necessary.

Medihaler-Iso™

Riker brand of isoproterenol HCl 0.25% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.06 mg. isoproterenol. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Note: First prescription for Medihaler medications should include the desired medication *and* Medihaler Oral Adapter.



when blood pressure must come down

increased antihypertensive benefits

Lowering of diastolic and systolic pressures
Beneficial bradycardia
Increase in renal blood flow

low dosage of Apresoline

Combined with Serpasil, Apresoline is effective at an average daily dose of only 200 mg. Thus, side effects such as headache and tachycardia seldom occur.

versatility

Easier management of hypertension is made possible by two tablet strengths of Serpasil-Apresoline.

All patients to be given Serpasil-Apresoline may benefit from priming with Serpasil.

SERPASIL-APRESOLINE *Tablets #2* (standard-strength, scored), each containing 0.2 mg. of Serpasil and 50 mg. of Apresoline hydrochloride; *Tablets #1* (half-strength, scored), each containing 0.1 mg. of Serpasil and 25 mg. of Apresoline hydrochloride.

Serpasil®-Apresoline®

hydrochloride

(reserpine and hydralazine hydrochloride CIBA)

COMBINATION TABLETS